

## TOWARDS STANDARDIZED REPORTING IN STUDIES OF ENCAPSULATING PERITONEAL SCLEROSIS

Encapsulating peritoneal sclerosis (EPS), a serious but uncommon complication of peritoneal dialysis (PD), initially well described in the Japanese patient population (1–3), is now widely recognized. Because of the severe morbidity and mortality attached, EPS has the potential to negatively affect perceptions of the value of PD as a long-term therapy and so affect the take-on rate and increase early transfer to HD. It is now well established that EPS is strongly associated with duration of PD therapy (4,5), with ultrafiltration failure associated with membrane fibrosis (6,7), and also, paradoxically, with stopping PD. Nevertheless, significant deficits in the understanding of EPS remain. That lack of understanding is implicit in nonspecific diagnostic criteria and an uncertain association with peritonitis, issues that arise in a study by Wong *et al.* (8) in this issue of *Peritoneal Dialysis International*.

### WHAT ARE THE DIAGNOSTIC CRITERIA CURRENTLY, AND HOW HAVE THEY BEEN APPLIED?

The current International Society for Peritoneal Dialysis diagnostic criteria are set out in a review by Kawaguchi *et al.* (9) and are based on two factors: symptoms suggestive of bowel obstruction, and either surgical or radiologic evidence of peritoneal thickening or cocooning as a cause of the symptoms. Disturbance of normal intestinal function was emphasized, but clear obstruction was not specified as a necessity. Symptoms mentioned included abdominal pain, nausea, vomiting, weight loss, fullness, and anorexia, although the severity of these manifestations can be variable. Although the diagnosis at laparotomy is usually apparent, the radiologic criteria have subsequently been refined and evaluated in numerous studies. It is apparent from the published literature that application of these diagnostic criteria has varied considerably.

The largest case series of EPS comes from a retrospective London-wide “Pan-Thames” study, in which 33% of 111 patients were reported to have obstruction; 67%, abdominal pain; 59%, vomiting; and 39%, ascites. Only 20% were reported to have weight loss, but 39 of the 111 were receiving parenteral nutrition. Mortality was 53%, with a median time to death of 7 months (10).

Summers *et al.* (11) published a single-center retrospective case series from what is now one of the two designated UK surgical centers for EPS. Of 27 patients, 16 had severe disease, with 6 cases of complete obstruction. The remaining 11 were classified as having “mild to moderate” disease, but the authors explicitly state that the division was arbitrary. Among the latter 11 patients, 3 had features of EPS on computed tomography (CT), but with no symptoms; the others had symptoms not requiring surgery.

To minimize diagnostic heterogeneity in a Dutch series of 62 patients, only patients with persistent or recurrent obstruction together with radiologic or macroscopic evidence were included (12). In the single-center Stoke PD cohort, 2 of 11 patients with EPS were considered to present slightly differently, their EPS being associated with early and severe infectious peritonitis (6).

Based on a comparative analysis of CT images from 27 EPS patients, 15 hemodialysis patients, and 20 PD patients with a mean dialysis duration of 4.0 years, a scoring system was developed based on quantifying the degree of 6 different findings. The resulting scores differentiated the groups well and produced good interobserver agreement; however, CT scores did not necessarily reflect disease activity (13).

In a review from Amsterdam of CT images, 15 patients with EPS were compared with 16 control subjects with a mean PD duration of 62 months (14). Of the control subjects, 10% or more showed peritoneal enhancement; 12.5% or more, peritoneal calcification; and 18.7% or more, peritoneal thickening. Only 1 (6.3%) had obstruction. Notably, the authors considered non-resolving peritonitis to be an indicator of EPS. In another study of 20 EPS patients by Goodlad *et al.* (15), CT images from several months before a formal EPS diagnosis were reviewed. Compared with asymptomatic patients, those who were symptomatic had a significantly higher validated EPS CT score, but neither group was considered at the time to have EPS.

Several further studies have clearly identified patients with an abnormal pathologic process (sometimes associated with symptoms), among whom at least some have gone on to develop what the study authors consider to be “full-blown” EPS. However, because of the lack

of more-specific diagnostic criteria, it is not possible to compare these groups because each study relied on the authors' own perceptions of what constitutes "full-blown" EPS.

#### WHAT IS THE ROLE OF PERITONITIS IN EPS?

Early publications frequently cite peritonitis as a risk factor for EPS, but the potential role that peritonitis might play in EPS is complex. First, peritonitis is a common reason for stopping PD, and stopping PD appears to be a risk factor. Second, a high frequency of peritonitis over a prolonged period might contribute to membrane damage accrued during long-term PD. Third, peritonitis might act as an acute precipitant of EPS (a "second hit") in patients with fibrosed, damaged membranes. Fourth, EPS might present as a sterile peritonitis (an "inflammatory stage"), with or without an infectious trigger. And finally, EPS patients with ascites might develop spontaneous bacterial peritonitis.

The first issue is suggested by the fact that many case series report EPS more often developing after PD has stopped (10–12), possibly because of local accumulation of inflammatory or fibrotic signaling molecules. However, no studies have examined whether typical infectious peritonitis is over- or under-represented as a reason for stopping PD in patients who subsequently developed EPS compared with other patients without EPS matched for duration of PD.

The second issue has been examined most robustly in an ANZDATA study, in which peritonitis was not associated with EPS (16). That finding was replicated in other recent case series (6,11), with the EPS group actually having a significantly lower overall peritonitis rate in some cases (12). The likely reason for this counterintuitive finding may be the risk associated with stopping PD early if the peritonitis risk is higher.

The third issue has been only partially addressed in the past. A small study by Bilgic *et al.* (17) suggested that patients stopping PD for peritonitis were more likely to develop intra-abdominal collections, which themselves are associated with systemic inflammation; however, that study did not specifically address EPS. Another study by Szeto *et al.* (18) addressed intra-abdominal collections after peritonitis requiring catheter removal. In 24 patients with available CT imaging, features compatible with EPS were present: peritoneal enhancement in 12.5%, peritoneal thickening in 45.8%, peritoneal calcification in 4.2%, bowel-wall thickening in 12.5%, adhesions in 58.3%, and signs of obstruction in 16.7%. None of the patients were considered to have EPS despite the fact that 2 were subsequently admitted with obstruction.

Very few published data are available to inform the fourth and final questions, aside from inferences from histologic work to address the fourth question.

#### WHAT DOES THIS LATEST STUDY ADD?

The single-center retrospective study by Wong *et al.* of 62 patients who had catheter removal for refractory peritonitis identified 39 "high risk" patients who were considered to have a persistent sterile peritonitis and 23 others in whom peritonitis resolved after catheter removal and who acted as a control group. Evidence of persistent peritonitis included continued systemic inflammation and the presence of intra-abdominal collections that were often bloodstained and always sterile on multiple paracenteses.

One important weakness of the study is its failure to report leukocyte counts in the collections (in EPS, blood-stained ascites is usually free of leucocytes). Compared with the control group, the group designated high risk also had other features typically expected of an EPS cohort, with longer duration of PD, faster peritoneal solute transport rates, and most importantly, CT features and symptoms of EPS. Of the high-risk group, 12 went on to develop "full-blown" EPS at a mean of 37 days after catheter removal, and those 12 were compared with the rest of the high-risk group. No significant differences were found, although a trend toward faster solute transport and ultrafiltration failure was observed in this study with very small numbers to support such an analysis.

The authors have therefore partly addressed the fourth question concerning the role of peritonitis in EPS by describing, with greater clarity than previously, a distinct presentation of EPS in which a non-resolving peritonitis is presumably precipitated by infectious peritonitis requiring catheter removal. Their patient group also had a relatively fast transition to obstructed EPS after catheter removal. The mean onset of 37 days is a finding similar to that in the London case series, in which the overall mean time to EPS after PD catheter removal was 5.5 months, but in which the progression to EPS occurred within 3 months for 17 of 20 patients whose catheter was removed for peritonitis.

Unfortunately, Wong *et al.* missed an opportunity to compare either their high-risk group or the "full blown" EPS subgroup to the rest of the EPS patients at their center, which would have helped to define how distinct their study group was. They could also have confirmed the culture-negative rate of the precipitating—presumed infectious—peritonitis.

What they have also done, however, is to also illustrate the variability in the diagnosis of EPS. The high-risk

group as a whole had a mean Tarzi CT score of 7.69, and all had symptoms compatible with EPS. Nevertheless, the authors felt that these factors were not sufficient to diagnose EPS. Based on existing case series, it seems

highly likely that other authors would have described these patients as having EPS. As such, this study by Wong and colleagues could also be viewed as examining EPS patients for predictors of subsequent obstruction.

TABLE 1  
Suggested Structure for Reporting of Encapsulating Peritoneal Sclerosis (EPS)

Domain	Details
Radiologic	Computed tomography score as suggested by Tarzi <i>et al.</i> (see Table 2). It would be desirable to include the scores for each of the individual findings <sup>a</sup> . The presence or absence of peritoneal enhancement should also be reported.
Macroscopic appearance of encapsulation (19)	<ol style="list-style-type: none"> <li>1. Sticky fibrin coating lies atop the EPS membranes containing the brown and thick peritoneum, with inter-enteric sclerotic membranes</li> <li>2. Cobweb-like inter-enteric sclerotic cover</li> <li>3. Classical intestinal cocooning with a sclerotic capsule</li> </ol>
Intra-abdominal extent (20)	Sclerosis or tanning of small bowel: <ul style="list-style-type: none"> <li>• Entire length or a section of bowel</li> <li>• Entire circumference or anti-mesenteric border</li> </ul> Encapsulation: <ul style="list-style-type: none"> <li>• Localized or widespread</li> </ul> Calcification: <ul style="list-style-type: none"> <li>• Isolated small plaques or large areas</li> </ul>
Histologic appearance (21)	Presence of <ol style="list-style-type: none"> <li>1. Podoplanin</li> <li>2. Fibroblast-like cells</li> <li>3. Mesothelial denudation</li> <li>4. Calcification</li> <li>5. Acellular areas</li> <li>6. Fibrin deposits</li> <li>7. Fibrosis</li> <li>8. Vasculopathy</li> <li>9. Acute inflammation</li> <li>10. Chronic inflammation</li> </ol>
Symptomatology	<ol style="list-style-type: none"> <li>1. Asymptomatic</li> <li>2. Mild symptoms (occasional pain, nausea, or even vomiting that does not require intervention or lead to a decline in nutrition)</li> <li>3. Intermittent or mild-to-moderate obstructive symptoms (sufficient to contribute to undernutrition and weight loss—for example, because of food avoidance, pain, or episodes of vomiting that resolve without intervention)</li> <li>4. Complete or severe persistent obstructive symptoms that require intervention (surgery, drip and suck, parenteral nutrition)</li> </ol>
Peritonitis or inflammation	Report occurrence of any of <ol style="list-style-type: none"> <li>1. Peritonitis causing cessation of peritoneal dialysis</li> <li>2. Sterile prolonged peritonitis</li> <li>3. Ascites without a raised white cell count</li> <li>4. Significant systemic inflammation</li> </ol>

<sup>a</sup> The computed tomography score proposed by Tarzi *et al.* (13) was selected because it provides more details on the areas it covers and because the division of bowel-wall thickening into small and large bowel by Vlijm *et al.* (14) produced scores that did not perform well at distinguishing EPS patients from control subjects, with poor consistency between observers. In the latter study, peritoneal enhancement did appear to perform well and so should also be reported.

TABLE 2  
Features of the Computed Tomography Scoring System<sup>a</sup>

Score	Peritoneal calcification	Peritoneal thickening	Bowel-wall thickening	Bowel tethering	Loculation	Bowel dilatation
0	Not identified	Not identified	Not identified	Not present	Not present	Not identified
1	Localized area (<20%)	Localized area (<20%)	Localized bowel	Mild tethering	<3 Locules	Localized bowel
2	20% of peritoneum	20% of peritoneum	20% of bowel	Moderate tethering	3–6 Locules	20% of bowel
3	50% of peritoneum	50% of peritoneum	50% of bowel	Marked tethering	Multiloculated	50% of bowel
4	Extensive (>80%)	Extensive (>80%)	Extensive (>80%)			Extensive (>80%)

<sup>a</sup> Tarzi *et al.* (13).

#### WHAT CAN WE DO ABOUT THE DIAGNOSTIC VARIABILITY?

Bearing in mind the large number of unanswered questions concerning EPS, there is a clear need to standardize the reporting of EPS cases so that it is clear which group of patients a study has incorporated and therefore how to interpret the findings. The easiest way of ensuring that cases of EPS are unequivocal is to stipulate that cases must have a severe form of obstruction—a strategy used by at least two recent studies, but likely to lead to under-reporting of the problem, leaving many of the remaining questions concerning EPS unaddressed. For studies to be comparable and consistent, standardized reporting of details is necessary.

We suggest that studies should report all the findings covering the main features of EPS: that is, radiologic, surgical, and histologic findings; symptoms; the presence (or not) of peritonitis as defined by standard criteria; and local and systemic inflammation. Table 1 sets out one potential structure that could be used. The structures for macroscopic appearance of encapsulation and intra-abdominal extent are based on work reported in this issue of *Peritoneal Dialysis International* (19,20), the radiologic structure is based on work by Tarzi *et al.* (10) and Vlijm *et al.* (14), and the histologic criteria are based on work by Braun *et al.* (21). As more data emerge, the structure can be refined iteratively.

We also suggest that studies should be quite clear, based on the foregoing features, which criteria they used to diagnose EPS: that is, the CT score or the criteria used if radiologic findings were considered important, how the presence of peritonitis was viewed, the level of symptoms that were considered necessary, and whether surgical findings were considered important, with a clear description of what was considered EPS based on the outlined structure. Furthermore, given that the natural history of

EPS is still not exactly clear, we recommend that studies stipulate whether the diagnostic criteria were applied based on initial presentation or subsequent progression. If the diagnosis was not made at initial presentation, then information on which of the EPS features were present at that time should also be provided, if available.

We believe that this kind of approach will allow for a clearer picture of the natural history of EPS to emerge and for better comparability between studies. It will also provide a structure to investigate issues such as the role of inflammation.

#### DISCLOSURES

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