

Encapsulating Peritoneal Sclerosis (EPS)

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EPS: Outline

- Definition and epidemiology
- Clinical presentation
- Imaging
- Pathology
- Treatment
- Outcomes
- Summary

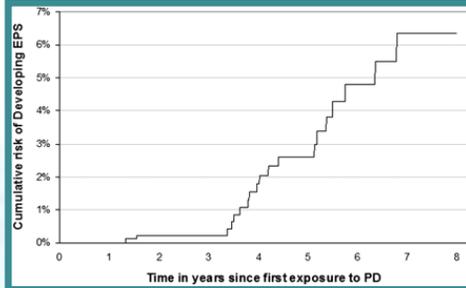
Encapsulating Peritoneal Sclerosis (EPS)

- Rare complication but serious complication of peritoneal dialysis (PD):
 - First described in 1980 (1)
 - Incidence varies between 0.5 to 4.4% (2-8)
 - Associated with significant morbidity and mortality
 - Many present after PD has been discontinued
 - The diagnosis requires both the:
 - Clinical features of intestinal obstruction or disturbed gastrointestinal function
 - Evidence of bowel encapsulation either radiologically or pathologically

ISPD guidelines from 2000 (2), felt the term encapsulating peritoneal sclerosis (EPS) more accurately described the morphologic changes seen in this disorder. Other terms used to describe this entity include (8,9):

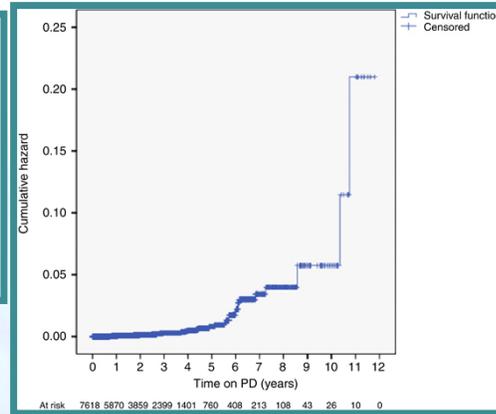
- Peritoneal fibrosis
- Peritoneal sclerosis
- Sclerotic thickening of the peritoneal membrane
- Sclerotic obstructive peritonitis
- Calcific peritonitis
- Encapsulating peritonitis
- Peritoneal chronica fibrosa incapsulata
- Abdominal cocoon
- Sclerosing peritonitis

Incidence of EPS



SCOTLAND
1238 pts (1/1/2000-12/31/2007)
46 cases
8-year cumulative incidence, 8.1%

Brown et al, Clin J Am Soc Nephrol 2009; 4: 1222-9
Johnson et al, Kidney Int 2010; 77: 904-12



Australia and New Zealand
7618 pts (1/1/1995-12/31/2007)
33 cases
8-year cumulative incidence, 3.9%

The incidence of EPS varies across the globe. It has been reported to vary between 2.1% to 19.4% for patients maintained on PD for 5-8 years. Factors that may contribute to this variation in the published literature include: patient numbers in the study, single center vs registry data, retrospective vs prospective, prevalent vs incident patients, criteria to establish the diagnosis and potential true differences in incidence. However, the observed incidence of EPS increases across all studies with length of time on PD. This slide demonstrates this in the ANZDATA registry (4) and Scottish Renal Registry (10) data. It should be stressed as reported in the ISPD position paper that most patients on PD for a long duration do not develop EPS (2).

EPS: Risk Factors

- The only consistent risk factor is duration on peritoneal dialysis
- Other potential factors
 - Glucose exposure
 - Inflammation – peritonitis
 - Chemical exposure
 - chlorhexidine
 - Genetic factors
 - Various other factors unrelated to peritoneal dialysis

EPS: Clinical Manifestations

- Symptoms of bowel obstruction
 - Persistent/intermittent
 - Partial/complete
 - Abdominal pain/distention/nausea/vomiting
- Abdominal mass
- Hemoperitoneum
- Malnutrition and failure to thrive
- Ultrafiltration problems

The symptoms of EPS can be vague, intermittent or chronic, and mild or severe. Kawanishi et al (11) proposed four stages of ESP: pre-symptomatic; inflammatory; encapsulating and ileus to potentially target therapeutic tactics for EPS. Other disease processes need to be excluded that can present with similar symptoms. The clinical manifestations of EPS can also develop after the patient is transferred from peritoneal dialysis to hemodialysis or after receiving a kidney transplant. Loss of ultrafiltration and an increase in peritoneal membrane small solute transport has been found in many EPS patients, but this is neither sensitive nor specific. Thus, a constellation of clinical symptoms is not sufficient to make the diagnosis of EPS, but a high index of suspicion is required so an early diagnosis can be pursued.

EPS: Radiologic Manifestations

- **Ultrasound Evaluation:**
 - Classical trilaminar appearance of the bowel wall with PD fluid in abdomen
 - Abnormal small bowel peristalsis (small bowel dilation)
 - Matted bowel loops with tethering to posterior abdominal wall
 - Membrane formation anterior to bowel loops
 - Loculated Ascites
- **CT abdomen:**
 - Isolated peritoneal thickening or calcification is not enough
 - Need to look for constellation of findings
 - Diagnostic imaging modality of choice

CT Scan Findings in EPS

Tarzi et al	Vlijm et al
Peritoneal thickening	Peritoneal thickening
Peritoneal calcification	Peritoneal calcification
	Peritoneal enhancement
Bowel wall thickening	
Bowel tethering	Adhesions of bowel loops
Bowel dilatation	
	Signs of bowel obstruction
Loculation (ascites)	Fluid loculation/septation
CT score 0-4 for each except bowel tethering and loculation (scored 0-3); range 0-22	Presence of three of above six items
Median score: pts, 9; PD controls, 1; HD, 0	Sensitivity, 79-100%; Specificity, 88-94%

*Tarzi et al, Clin J Am Soc Nephrol 2008, 3: 1702-10
Vlijm et al, Perit Dial Int 2009; 29: 517-22*

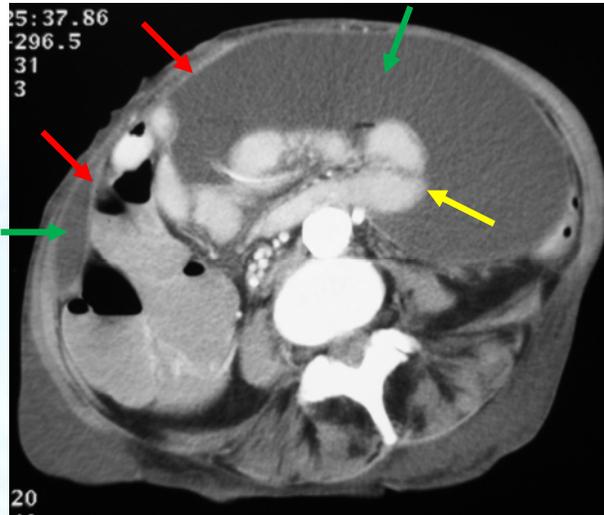
Abdominal imaging has been used to confirm the diagnosis of EPS, however until recently there was no consensus on its specific radiologic abnormalities. Two groups examined the use of CT findings characteristic for EPS and assessed the reliability and diagnostic utility of these findings (12,13). The scoring systems used in both studies were able to separate a significant difference between a higher score in patients with EPS from those of controls. However, some of the control patients on PD in both studies did have some of the CT findings considered characteristic of EPS. None of these controls went on to develop EPS. In Tarzi's study (12), the HD control group did not have any of the CT findings suggestive of EPS. It is of interest that the total CT scan score did not correlate with the clinical outcome in patients with EPS.

Another study looking at the incidence and experience of EPS in patients maintained on PD for ≥ 5 years from a single center in the US found CT abnormalities as described by Tarzi in 66% of patients with available CT scans (14). Only 10/25 of these patients had clinical symptoms of EPS. The other 15 patients did not develop EPS on follow up. These findings underscore the importance of utilizing the ISPD criteria (2,9) to diagnose EPS.

Tarzi et al (12) also examined available pre-diagnostic CT scans done a median of 1.5 years before the diagnosis of EPS was made. Pre-diagnostic studies in 9/13 patients were normal or near-normal.

The next few slides are examples of the CT findings used in the above scoring systems.

CT Findings of EPS



Thickened Enhancing Peritoneum (**arrows**)

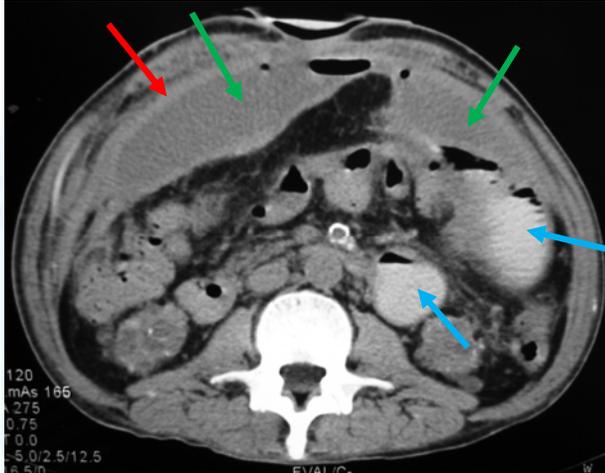
Loculated Fluid Collection (**arrows**)

Tethered small bowel Loops (**arrows**)

Cameron et al: American Roentgen Ray Society Annual Meeting, 2010

In Tarzi's study (12), each parameter analyzed showed a significant difference between patients with EPS and controls. Bowel tethering and peritoneal calcification were the most specific parameters. The presence of loculations was the least specific parameter.

CT Findings of EPS



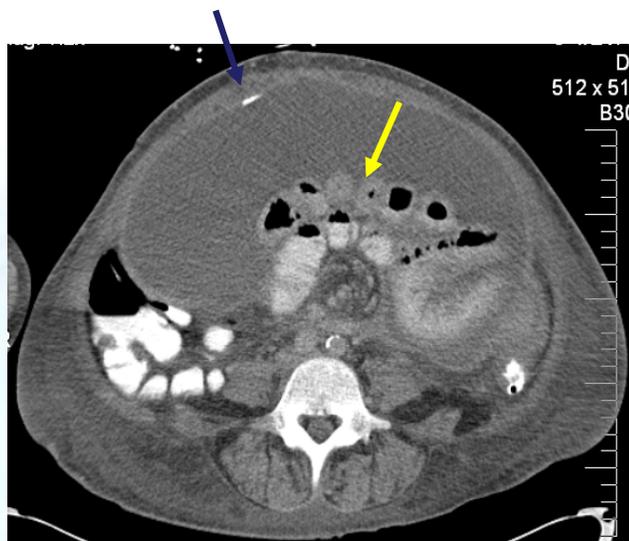
Dilated and thick-walled loops of small bowel filled with fluid and oral contrast (**arrows**).

Peritoneal thickening (**arrow**).

Loculated fluid collections (**arrows**).

Cameron et al: American Roentgen Ray Society Annual Meeting, 2010

CT Findings of EPS

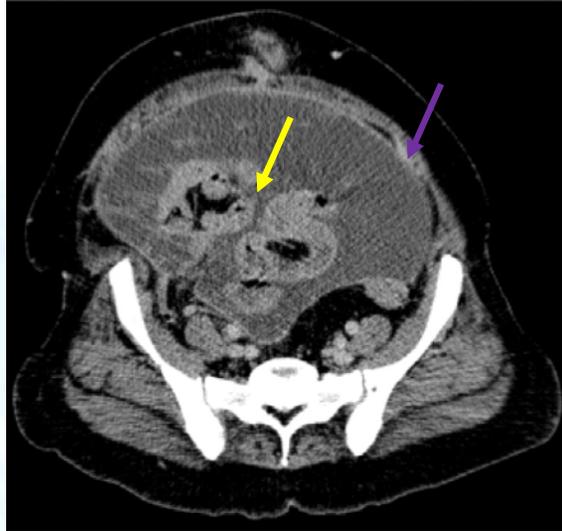


Bowel Tethering
(**arrow**)

Peritoneal
calcification (**arrow**)

Cameron et al: American Roentgen Ray Society Annual Meeting, 2010

CT Findings of EPS



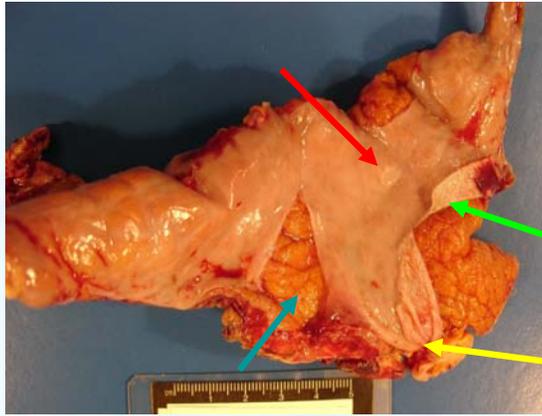
Tethered bowel
Loops (arrows)

Peritoneal
Enhancement (arrow)

Vlijm et al, Perit Dial Int 2009; 29: 517-22

In Vlijm's report (13) peritoneal enhancement was found to be very specific for EPS. Based on this, the authors suggested that a CT with contrast enhancement would be preferred.

Gross Pathologic Findings of EPS



Peritoneal thickening
(arrow)

Peritoneal
inflammatory changes
(arrow)

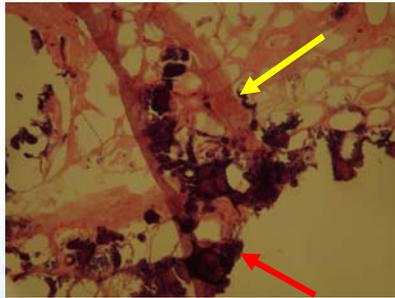
Peritoneal
calcifications (arrow)

Omental fat (arrow)

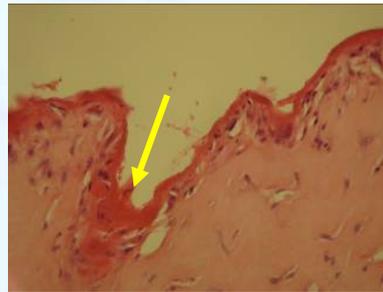
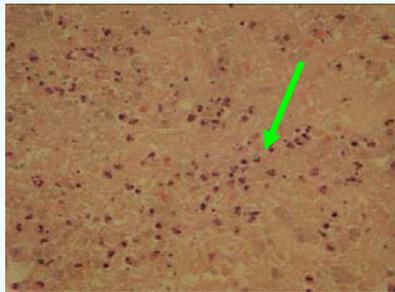
Cameron et al: American Roentgen Ray Society Annual Meeting, 2010

Characteristic findings at laparotomy, laparoscopy or autopsy can range from the formation of a thin membrane on the visceral and/or parietal peritoneum to cocoon-like encapsulation of the entire intestine found with advanced cases. Various degrees of peritoneal thickening and calcification may be seen. Fibrous bands can form between loops of bowel. Small loculated abscesses may also be seen due to local perforation (16).

Histology of EPS



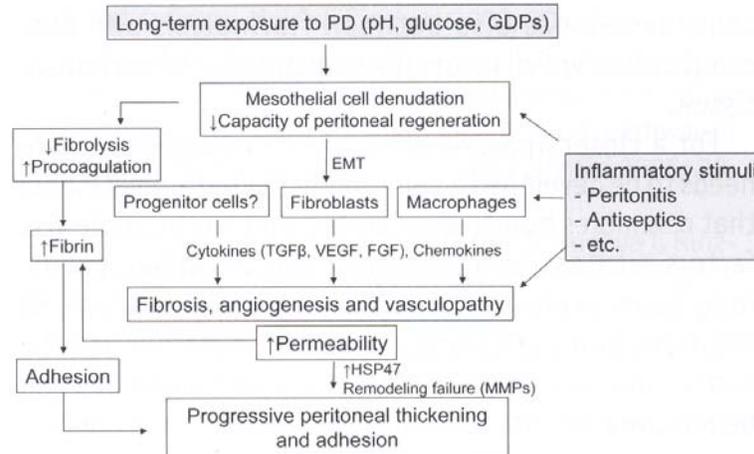
Peritoneal thickening and fibrosis (arrows)
Peritoneal calcification (arrow)
Inflammatory cells - neutrophils/lymphocytes (arrow)



Cameron et al: American Roentgen Ray Society Annual Meeting, 2010

Patients with a long history of PD can have peritoneal changes that are referred to as peritoneal sclerosis. The changes seen histologically include mesothelial denudation, interstitial fibrosis and a microvasculopathy (17). Some of these changes are seen as well in EPS. However, not all patients with peritoneal sclerosis will develop EPS. Fibrin deposition, caused by increased plasma exudation from peritoneal microvessels, is the most characteristic feature of EPS. Honda et al (16), examined specific histologic findings and immunohistochemical markers from peritoneal biopsy specimens from patients with and without the diagnosis of EPS. Differentiation of EPS from other inflammatory conditions using immunohistochemical analysis alone was not discriminating. They found higher frequencies of the following findings in the EPS group and propose these histologic findings for a diagnosis of EPS: fibrin deposition, fibroblast swelling, capillary angiogenesis, mononuclear cell infiltration and presence of several immunohistochemical markers for peritoneal fibroblast activation and proliferation. Again, these criteria are not specific to EPS, but with macroscopic findings and the presence of clinical symptoms the diagnosis can be made.

Proposed Pathogenesis of EPS



Park et al: Perit Dial Int 2008; 28 (S5): S21-28

This slide illustrates the complex proposed pathogenesis of EPS based on data from experimental animal models of EPS (18). Other groups have proposed similar schema based on clinical studies and translational research (16,19). Increased time on PD leads to peritoneal membrane changes such as mesothelial denudation, interstitial fibrosis, vasculopathy and angiogenesis, which may set the stage for the development of EPS. It is proposed that inflammatory stimuli (a “second hit”) superimposed on this altered peritoneal membrane may act as the inciting factor to trigger the onset of EPS. An epithelial to mesenchymal transformation occurs in the mesothelium and results in the release of cytokines and growth factors. This leads to inflammation, angiogenesis and ultimately fibrosis. Fibrin that exudates from the plasma and defective fibrinolysis, contributes to progressive intestinal adhesions and peritoneal thickening. From this proposed model, it can be seen why anti-inflammatory and anti-fibrotic drugs have been used therapeutically to treat EPS.

EPS: Management

- Supportive therapy (*ileus*):
 - Aggressive nutritional support
- Medical Therapy:
 - Tamoxifen (*anti-fibrotic*)
 - Immunosuppressive (*anti-inflammatory*)
- Surgical Intervention (*encapsulating*):
 - Partial or complete enterolysis,
 - Avoid enterotomy

After the diagnosis of EPS is made, PD should be discontinued and the patient transferred to HD, in most cases (8). Mild cases of EPS could potentially worsen after stopping PD, and patient related factors need to be taken into consideration. There are reports of patients being maintained on PD with () and without (14) specific therapy.

EPS can lead to severe malnutrition which is a crucial factor in the morbidity and mortality associated with EPS. Dietary referral is of the utmost importance, and parenteral nutrition is recommended for severe cases of EPS

Kawanishi et al (11) proposed four stages of ESP: pre-EPS; inflammatory; encapsulating and ileus to potentially target therapeutic options for EPS. Many of the therapeutic agents used target the inflammatory and/or fibrotic features of EPS. While corticosteroids, immunosuppressants and tamoxifen have been used to treat EPS, there is no clear evidence-based drug therapy for EPS. This is due to EPS being a rare condition coupled with the lack of randomized controlled trials of drug therapy. The current literature is based on case reports or small observational series of drug therapy. It is of interest that EPS can develop following renal transplantation in patients already receiving steroids and other immunosuppressive medications, which would argue against the therapeutic benefit of these agents. Multi-center, randomized control trials are needed to further investigate potential therapeutic options

For recurrent or refractory bowel obstruction surgical therapy should be considered. In the past surgery was associated with high mortality rates. Referral to surgical units with expertise in EPS surgery has resulted in high rates of symptomatic improvement and survival (19,20).

EPS: Outcomes

	EPS Cases	Mortality (over study period)	Median Survival, months
Nomoto et al, '96	62	44%	-
Rigby et al, '98	54	56%	-
Lee et al, '03	31	26%	-
Kawanishi et al, '01	17	35%	11 (to death)
Kawanishi et al, '04	48	38%	-
Summers, '05	27	30%	-
Balasubramaniam, '09	111	53%	14
Brown, '09	46	57%	6
Johnson, '10	33	55%	48

Many deaths may not be related to EPS

The mortality of patients with EPS varies between 26-58%. It was also found that mortality increased with length of time on PD (6,22) Mortality differences among the studies can be due to different factors which include: different patient populations, different time periods, retrospective vs prospective, incident vs prevalent patients, and the definition of EPS. Many of the deaths reported were not due to EPS. In Johnson's study (4) there was no difference in mortality when those with EPS were compared with appropriate controls. Caution must be used when discussing optimal length of time on PD and risk of EPS.

EPS: Prevention

- No prospective data supporting a benefit of preemptively transferring long-term PD patients to HD
- Preserve residual renal function
- Try to minimize the use of high-glucose PD solutions
- Minimize episodes of peritonitis
- Await experience with “biocompatible” PD solutions

EPS: Summary

- Rare:
 - Most long-term patients will not develop the complication
 - Mandatory transition off PD after a pre-determined interval does not seem justified
- Diagnosis requires:
 - high index of clinical suspicion from clinical manifestations
 - constellation of CT or pathologic findings consistent with EPS
- Aggressive nutritional support, trial of medical therapy, and surgery in selected cases
- Outcomes better in contemporary cohorts?

EPS: References

1. Gandhi et al: Sclerotic thickening of the peritoneal membrane in Maintenance peritoneal dialysis patients. *Arch Int Med* 1980; 140:1201-1203.
2. Kawaguchi et al: Encapsulating Peritoneal Sclerosis: Definition, Etiology, Diagnosis, and Treatment. *Perit Dial Int* 2000; 20 (suppl 4): S43-55.
3. Rigby et al: Sclerosing peritonitis: the experience in Australia. *Nephrol Dial Transplant* 1998; 13: 154-159.
4. Johnson et al: Encapsulating peritoneal sclerosis: incidence, predictors, and outcomes. *Kidney Int* 2010; 77: 901-912.
5. Kawanishi H: Encapsulating Peritoneal Sclerosis in Japan: Prospective Multicenter Controlled Study. *Perit Dial Int* 2001; 21 (suppl 3): S67-S71.
6. Kawanishi et al: Encapsulating Peritoneal Sclerosis in Japan: A Prospective, Controlled, Multicenter Study. *Am J Kidney Dis* 2004; 44: 729-737.
7. Lee et al: Sclerosing encapsulating peritonitis as a complication of long-term continuous ambulatory peritoneal dialysis in Korea. *Nephrology* 2003; 8 (suppl) S33-S39.
8. Brown et al: Length of Time on Peritoneal Dialysis and Encapsulating Peritoneal Sclerosis: Position Paper for ISPD. *Perit Dial Int* 2009; 29: 595-600
9. Schmidt et al: Pathogenesis and Treatment of Encapsulating Peritoneal Sclerosis: Basic and Translational Research. *Perit Dial Int* 2008; 28 (suppl 5) S10-S15.
10. Brown et al: Encapsulating Peritoneal Sclerosis in the New Millennium: A National Cohort Study. *Clin J Am Soc Nephrol* 2009; 4: 1222-1229.

11. Kawanishi et al: Treatment options for encapsulating peritoneal sclerosis based on progressive stage. *Adv Perit Dial* 2001; 17: 200-4.
12. Tarzi et al: Assessing the Validity of an Abdominal CT Scoring System in the Diagnosis of Encapsulating Peritoneal Sclerosis. *Clin J Am Soc Nephrol* 2008; 3: 1702-1710.
13. Vlijm et al: Computed Tomographic Findings Characteristic for Encapsulating Peritoneal Sclerosis: A Case-Control Study. *Perit Dial Int* 2009; 29: 517-522
14. Gayomali et al: Incidence of Encapsulating Peritoneal Sclerosis: A Single-Center Experience with Long Term Peritoneal Dialysis in the United States. *Perit Dial Int* in press.
15. Cameron et al: Encapsulating Peritoneal Sclerosis – Imaging findings behind an under recognized complication of long-term peritoneal dialysis. American Roentgen Ray Society Annual Meeting 2010.
16. Honda et al: Pathology of Encapsulating Peritoneal Sclerosis. *Perit Dial Int* 2005; 25 (suppl 4) S19-S29.
17. Dobbie et al: Long-term effects of peritoneal dialysis on peritoneal morphology. *Perit Dial Int* 1994; 14 (suppl 3): S16-S20.
18. Park et al: Experimental Encapsulating Peritoneal Sclerosis Models: Pathogenesis and Treatment. *Perit Dial Int* 2008. 28 (suppl 5:) S21-S28.
19. Kawanishi et al: Recommendation of the Surgical Option for Treatment of Encapsulating Peritoneal Sclerosis. *Perit Dial Int* 2008; 28(suppl 3): S205-S210.
20. Kawanishi et al: Successful Surgical Management of Encapsulating Peritoneal Sclerosis. *Perit Dial Int* 2005; 25 (suppl 4): S39-S47.

21. Nomoto et al: Sclerosing Encapsulating Peritonitis in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis: A Report of the Japanese Sclerosing Encapsulating Peritonitis Study Group. *Am J Kidney Dis* 1996; 28: 420-427.
22. Summers et al: Single-center experience of encapsulating peritoneal sclerosis in patients on peritoneal dialysis for end-stage renal failure. *Kidney Int* 2005; 68: 2381-2388.
23. Balasubramaniam et al: The Pan-Thames EPS study: treatment and outcomes of encapsulating peritoneal sclerosis. *Nephrol Dial Transplant* 2009; 24: 3209-3215.
24. Nakamoto H: Encapsulating Peritoneal Sclerosis – A Clinician's Approach to Diagnosis and Medical Treatment. *Perit Dial Int* 2005; 25 (suppl 4): S30-S38.
25. Kawaguchi et al: Recommendations of the Management of Encapsulating Peritoneal Sclerosis in Japan, 2005: Diagnosis, Predictive Markers, Treatment, and Preventive Measures. *Perit Dial Int* 2005; 25 (suppl 4): S83-S95.
26. Woodrow et al: UK Encapsulating Peritoneal Sclerosis Clinical Practice Guidelines – July 2009. Produced by UK EPS Clinical Guidelines Group.

Question #1

- Which of the following is most consistent with the diagnosis of EPS?
 - A. 32 year old man on PD for 2 years presents with abdominal pain and cloudy fluid
 - B. 50 year old woman on PD for 5 years is found to have peritoneal thickening on a CT done for the evaluation of her lower back pain
 - C. 38 year old man on PD for 6 years who has lost weight in the setting of intermittent nausea and abdominal pain. A CT revealed peritoneal thickening/calcification and dilated small bowel.
 - D. 40 year old woman on PD for 3 years who has had persistent abdominal pain, nausea, vomiting and weight loss. A CT of her abdomen and pelvis was normal.

Question #1: Answer

- The correct answer is C. The diagnosis of EPS requires both the clinical features of the disorder and evidence of bowel encapsulation either radiographically or pathologically.

Question #2

- Which is the most consistent risk factor for the development of EPS?
 - A. Rapid transport status
 - B. Recurrent peritonitis
 - C. Ultrafiltration problems
 - D. Length of time on PD

Question #2: Answer

- The correct answer is D. The only consistent risk factor for EPS is duration on PD.

