CORSO

I PER-CORSI IN NEFROLOGIA E DIALISI

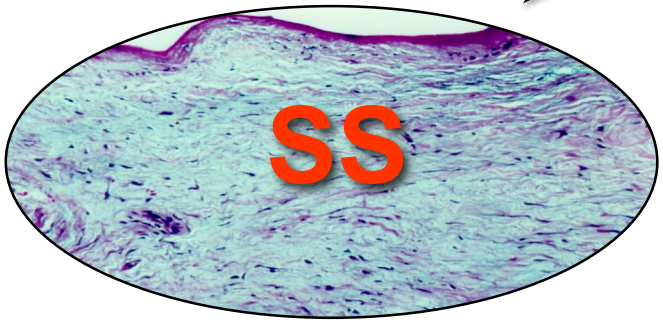
LE COMPLICANZE CRONICHE DEL TRATTAMENTO SOSTITUTIVO RENALE E DIALISI EXTRACORPOREA E DIALISI PERITONEALE IN PARTICOLARI CONTESTI

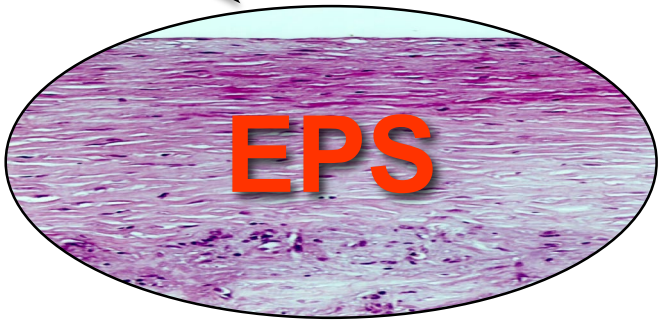
**17 maggio 2024**
**NH Hotel Pontevecchio**
**Lecco**

# La Peritonite Sclerosante Incapsulante (EPS)

**Guido Garosi**
**U.O.C. Nefrologia, Dialisi e Trapianto**
**Azienda Ospedaliero-Universitaria Senese**

# Sclerosi Peritoneale




**SS = Simple Sclerosis**

**EPS = Encapsulating Peritoneal Sclerosis**

Proceedings of the 1st Joint ISPD/EuroPD Congress
August 28 – 31, 2004, Amsterdam, The Netherlands
Peritoneal Dialysis International, Vol. 25 (2005), Supplement 3



**OPINION**

**ENCAPSULATING PERITONEAL SCLEROSIS IS A SEPARATE ENTITY: CON**

Masaaki Nakayama, Yukio Maruyama, and Miwako Numata

*Division of Kidney and Hypertension, Tokyo Jikei University School of Medicine, Tokyo, Japan*

**Due stadi della stessa patologia?**

**Due entità nosologiche separate?**

Proceedings of the 1st Joint ISPD/EuroPD Congress
August 28 – 31, 2004, Amsterdam, The Netherlands
Peritoneal Dialysis International, Vol. 25 (2005), Supplement 3



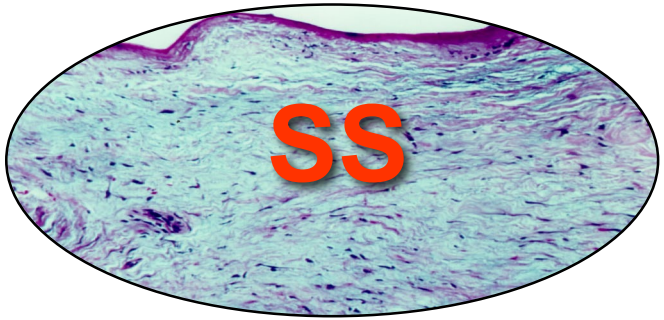
**OPINION**

**SCLEROSING PERITONITIS: A NOSOLOGICAL ENTITY**

Guido Garosi,[1] Nicola Di Paolo,[1] Giovanni Sacchi,[2] and Enzo Gaggiotti[1]

*UOC Nefrologia Dialisi e Trapianto,[1] Azienda Ospedaliera Universitaria Senese; Istituto di Neuroscienze,[2] Università di Siena, Siena, Italy*

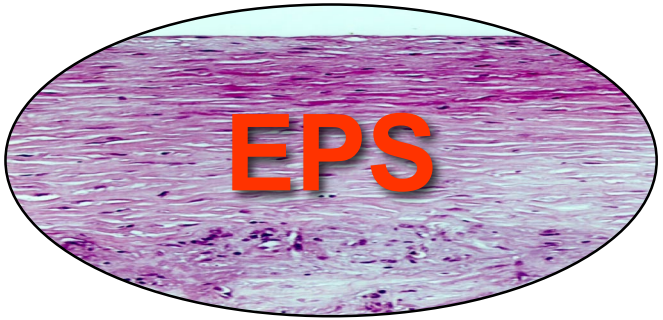
# Frequenza




**prevalenza 50 – 100 %**

**(dopo 6 – 24 mesi di DP)**

Rubin J et al, Am J Kidney Dis 1991;18:97
Schneble F et al, Pediatr Nephrol 1992;4:173
Garosi G et al, Semin Dial 2000;13:297
Williams JD et al, J Am Soc Nephrol 2002;13:470-479



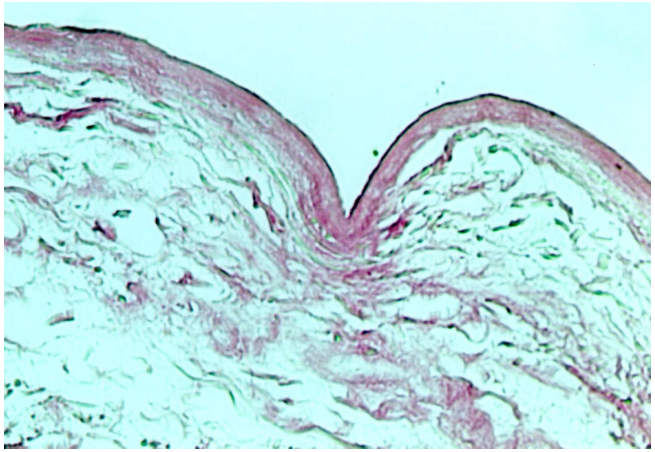

**prevalenza 0.5 – 2.8 %**

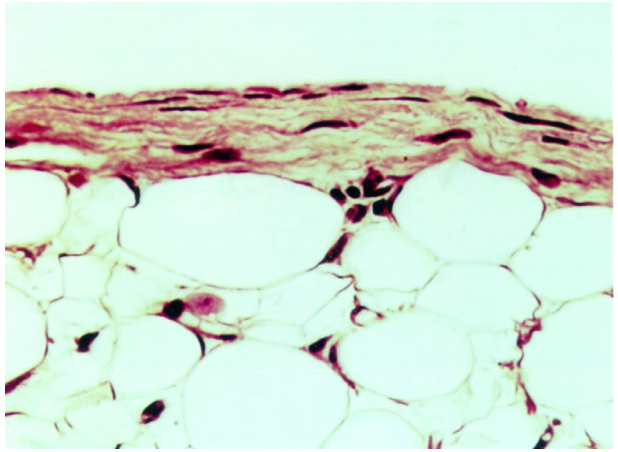
**incidenza 0 – 4.3**/1,000 anni paziente

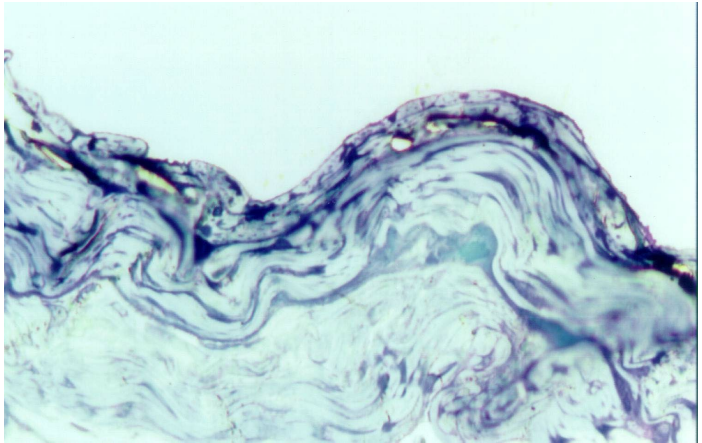
Nomoto Y et al, Am J Kidney Dis 1996;28:420
Afthentopoulos IE et al,Adv Renal Rep Ther 1998;5:157
Rigby RJ et al, Nephrol Dial Transplant 1998;13:154
Kawagushi Y et al, Perit Dial Int 2000;20(S4):S43
Nakayama M, Perit Dial Int 2001;21(S3):S72

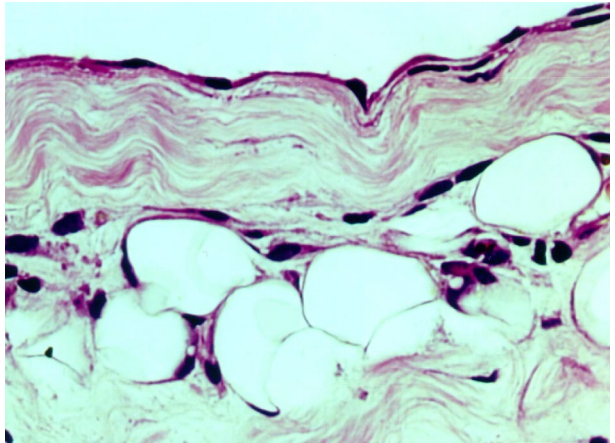
Simple Sclerosis is a thin (<40-50 micron) layer of submesothelial sclerotic tissue often limited to certain peritoneal areas, with monotonous histology

Garosi G, Di Paolo N J Nephrol 2001;14(S4):S30-38









Ronco C, Crepaldi C, Cruz DN (eds): Peritoneal Dialysis – From Basic Concepts to Clinical Excellence. Contrib Nephrol. Basel, Karger, 2009, vol 163, pp 45–53

# Different Aspects of Peritoneal Damage: Fibrosis and Sclerosis

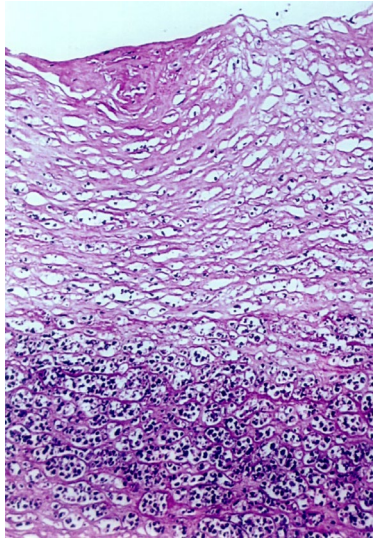
*Guido Garosi*

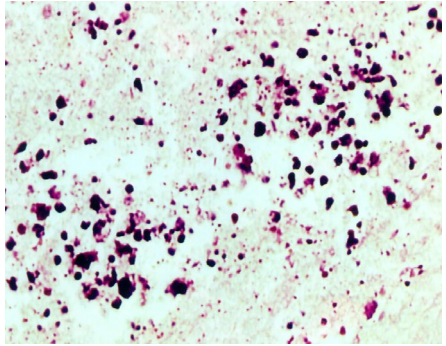
UOC Nefrologia, Dialisi e Trapianto, Azienda Ospedaliera Universitaria Senese, Siena, Italy

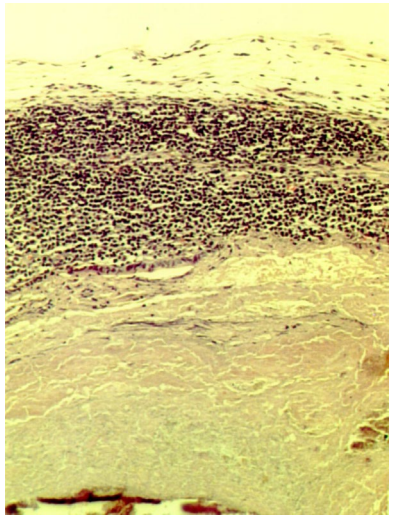
***Table 1.*** Pathology of SS and EPS (median and range; number of cases)

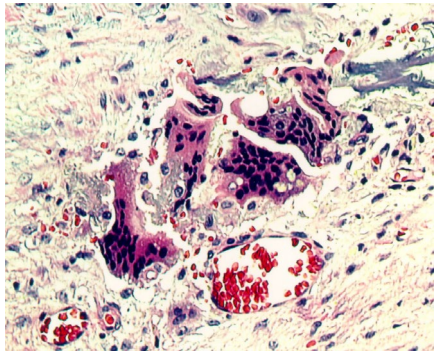
| | SS (n = 180) | EPS (n = 44) | p |
|---|---|---|---|
| Thickness of sclerosis, μm | 45 (10–70) | 750 (250–4,000) | <0.01 |
| Inflammation | 5/180 | 44/44 | <0.01 |
| Parvicellular infiltration | 5/180 | 40/44 | <0.01 |
| Mild | 5/180 | 0/44 | |
| Severe | 0/180 | 40/44 | |
| Microabscesses | 0/180 | 17/44 | <0.05 |
| Giant cells | 0/180 | 39/44 | <0.01 |
| Granulation tissue | 0/180 | 39/44 | <0.01 |
| Vascular alterations | 19/180 | 44/44 | <0.01 |
| Arterial thickening | 19/180 | 44/44 | <0.01 |
| Mild | 19/180 | 0/44 | |
| Severe | 0/180 | 44/44 | |
| Arterial occlusion | 0/180 | 41/44 | <0.01 |
| Arterial calcification | 0/180 | 26/44 | <0.01 |
| Arterial ossification | 0/180 | 9/44 | |
| Tissue calcification | 1/180 | 13/44 | <0.01 |
| Tissue ossification | 0/180 | 4/44 | |
| Presence of bone marrow | 0/180 | 2/44 | |

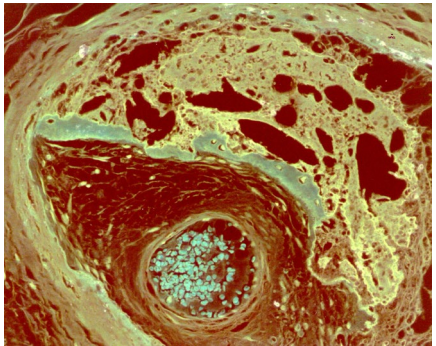
Statistical analysis: Mann-Whitney test (thickness of sclerosis), $\chi^2$ test (other variables).

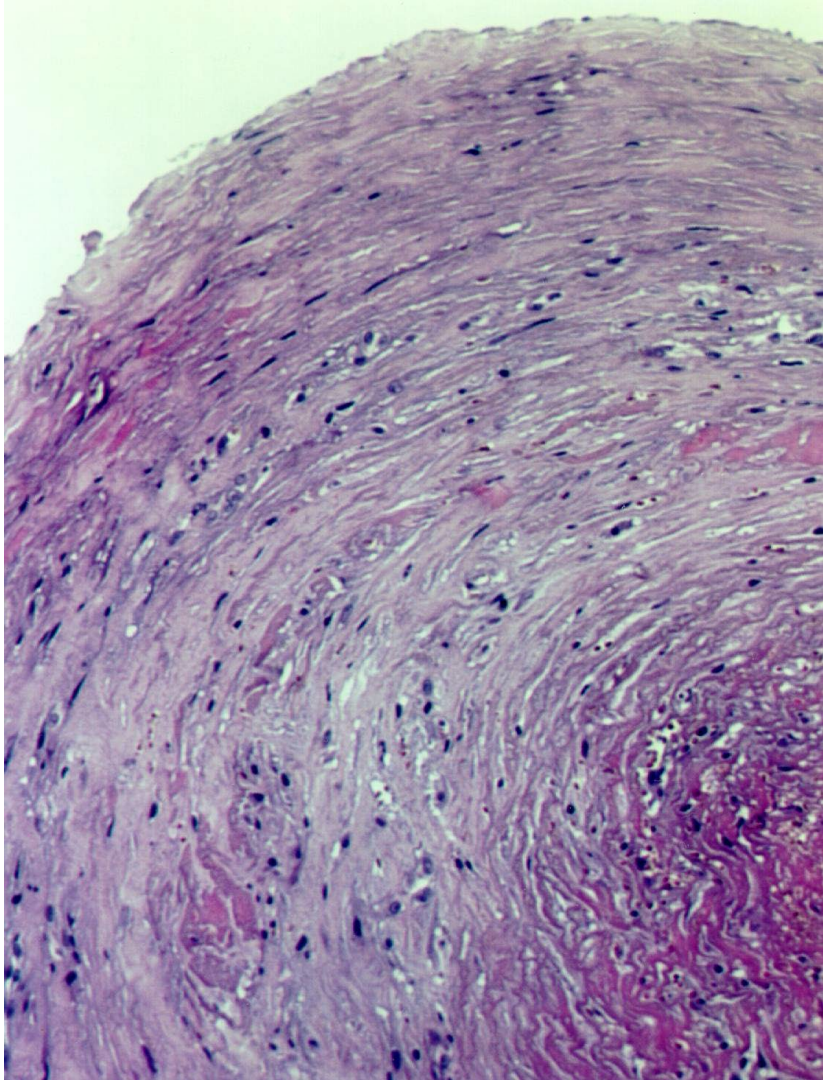


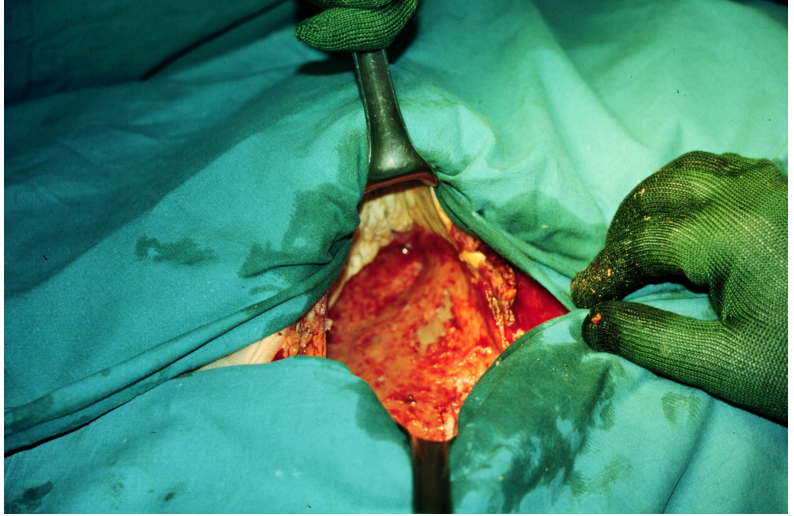


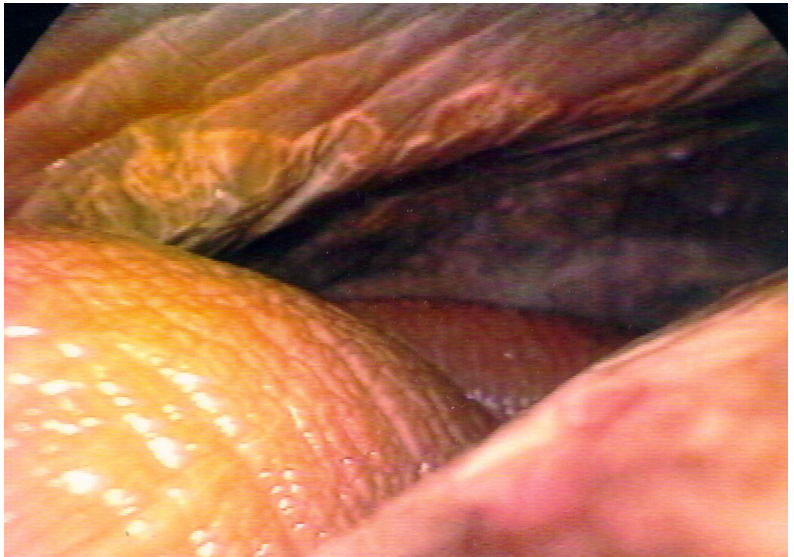




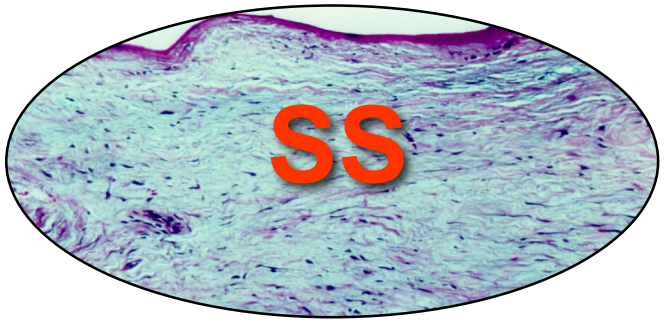


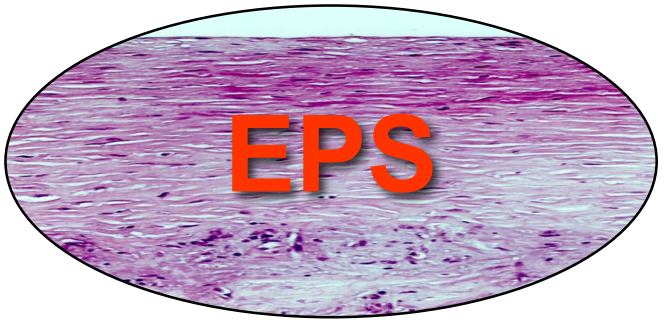






# Riproducibilità in modelli animali




**SI mediante dialisi**

**NO senza dialisi**

**Assenza di casi spontanei**

**NO mediante dialisi**

**SI senza dialisi**

**Presenza di casi spontanei**

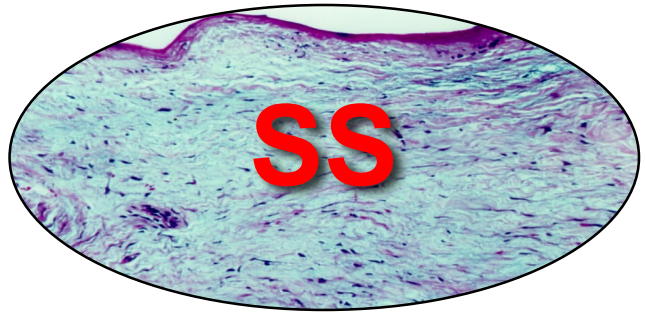

Wieczorowska K et al, Adv Perit Dial 1995;11:48
Di Paolo N et al, Perit Dial Int, 1995;15(7S):S61
Gotloib L et al, Perit Dial Int 1997;17(S2):S13
Garosi G et al, Perit Dial Int 1998;18:610-619

Brinkmann OA et al, Pathol Res Pract 1989;185:412-417
Friemann J et al, Pathol Res Pract 1990;186:117-123
Lee HG et al, Clin Exp Immunol 1995;100:139-144
Stabellini G et al, Int J Artif Organs 1998;21:87-94

# Eziologia

**Scarsa biocompatibilità della DP**

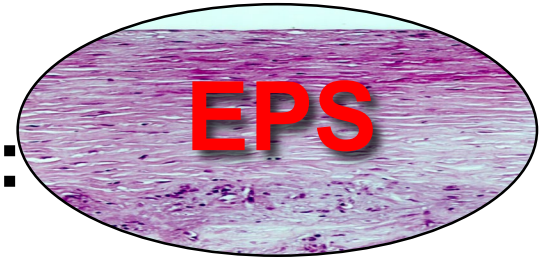
**- genti osmotici**
**- iperosmolarità**
**- basso pH**
**- tampone**





Jörres A et al, Int J Artif Organs 1992;15:79
Holmes CJ, Perit Dial Int 1993;13:88
Topley N et al, Perit Dial Int 1994;14(S3):S21
Breborowicz A et al, Am J Kidney Dis 1996;27:738
Devuyst O et al, Kidney Int 2000;58:1814-1815
Krediet RT et al, Perit Dial Int 2000;20(S4):S22-S42

# Eziologia

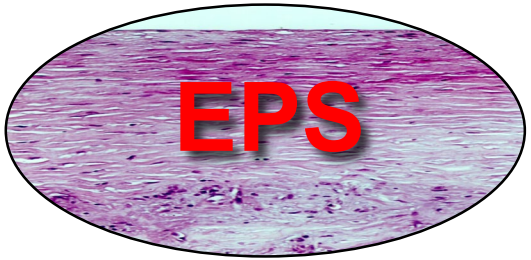



## Sconosciuta, solo fattori di rischio:

- durata della DP
- alti trasportatori
- scarsa biocompatibilità della DP
  - glucosio, pH, tampone, disinfettanti, catetere, filtri, plastiche, plasticizzanti
- peritonite

Nomoto Y et al, Am J Kidney Dis 1996;28:420
Afthentopoulos IE et al,Adv Renal Rep Ther 1998;5:157
Rigby RJ et al, Nephrol Dial Transplant 1998;13:154
Garosi G et al, Semin Dial 2000;13:297
Nakayama M et al, Adv Perit Dial 2002;18:131

# Eziologia




## Forme DP-indipendenti:

- β-bloccanti
- associazione con tumori

  cancro gastrico, tecoma ovarico, teratoma ovarico, carcinoma del pancreas, poliposi multipla, linfoma isticitico, carcinoma renale

- forme idiopatiche

  **patogenesi immune**

  associazione con interessamento generale del tessuto connettivo

  **predispositione genetica**

  elevata frequenza nelle donne di aree subtropicali

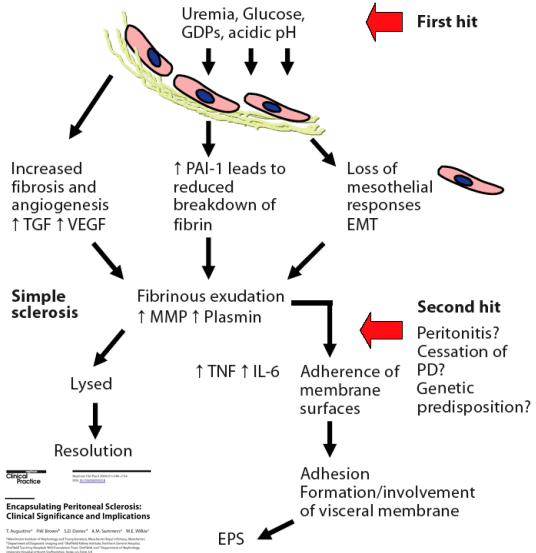
  Familial Multifocal Fibrosclerosis (Comings, 1967)

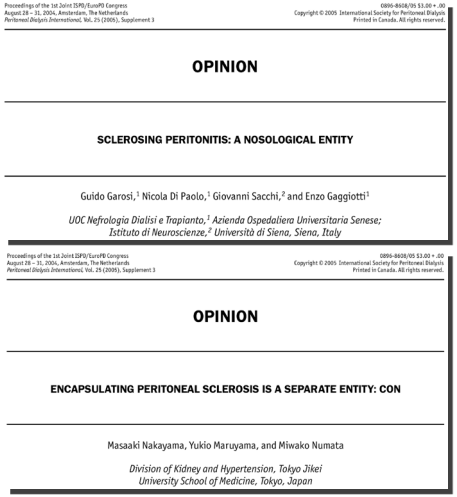
Nomoto Y et al, Am J Kidney Dis 1996;28:420
Afthentopoulos IE et al,Adv Renal Rep Ther 1998;5:157
Rigby RJ et al, Nephrol Dial Transplant 1998;13:154
Garosi G et al, Semin Dial 2000;13:297
Kawaguchi Y et al, Perit Dial Int 2000;20(S4):S43-S55

# EPS: patogenesi

## Accettazione della two-hit hypotesis:

## Simple Sclerosis e EPS come entità nosologiche diverse





OPINION

SCLEROSING PERITONITIS: A NOSOLOGICAL ENTITY

Guido Garosi,[1] Nicola Di Paolo,[1] Giovanni Sacchi,[2] and Enzo Gaggiotti[1]

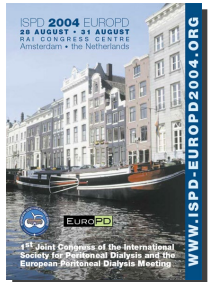
*UOC Nefrologia Dialisi e Trapianto,[1] Azienda Ospedaliera Universitaria Senese; Istituto di Neuroscienze,[2] Università di Siena, Siena, Italy*


OPINION

ENCAPSULATING PERITONEAL SCLEROSIS IS A SEPARATE ENTITY: CON

Masaaki Nakayama, Yukio Maruyama, and Miwako Numata

*Division of Kidney and Hypertension, Tokyo Jikei University School of Medicine, Tokyo, Japan*




# EPS: diagnosi

clinica

TC (scarso valore altre metodiche di imaging)

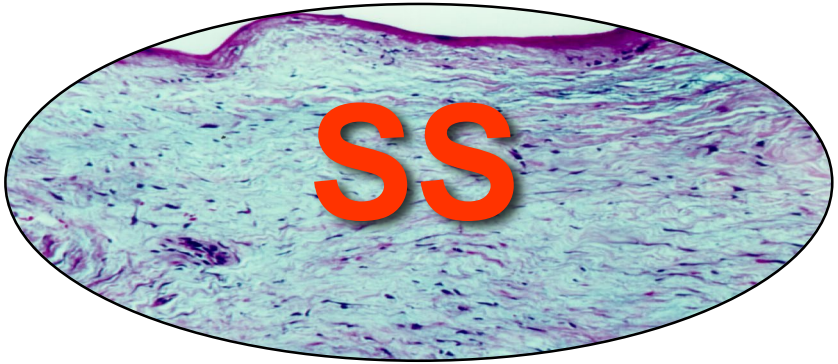
anatomia patologica

# EPS: diagnosi

- clinica

TC (scarso valore altre metodiche di imaging)

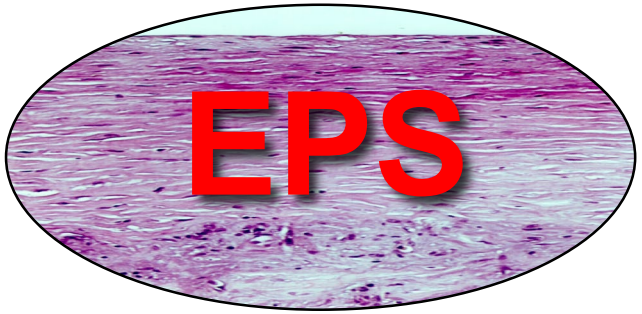
anatomia patologica




# nessuna manifestazione clinica

Dobbie JW et al, Perit Dial Int 1994;14(S3):S16
Grzybowski A et al, Przegl Lek 1997;54:52
Hendriks PM et al, Perit Dial Int 1997;17:136
Garosi G et al, Semin Dial 2000;13:297
Krediet RT et al, Perit Dial Int 2000;20(S4):S22-S42
Williams JD et al, J Am Soc Nephrol 2002;13:470

# Manifestazioni cliniche




**diminuita efficienza della DP**
**anoressia, nausea, vomito**
**diarrea, costipazione**
**Distensione addominale**
**febbre**
**perdita di peso**
**dolore addominale**
**effluente emorragico**
**ascite**
**masse addominali palpabili**
**ostruzione intenstinale incompleta o completa**

**mortalità > 50%**


Nomoto Y et al Am J Kidney Dis 1996;28:420
Rigby RJ et al, Nephrol Dial Transplant 1998;13:154
Afthentopoulos IE et al, Adv Ren Replace Ther 1998;13:221
Krediet RT et al, Perit Dial Int 2000;20(S4):S22-S42
Garosi G et al, Semin Dial 2000;13:297
Kawaguchi Y et al, Perit Dial Int 2000;20(S4):S43-S55

# EPS: diagnosi

clinica

→ TC (scarso valore altre metodiche di imaging)

anatomia patologica

# Assessing the Validity of an Abdominal CT Scoring System in the Diagnosis of Encapsulating Peritoneal Sclerosis

Ruth M. Tarzi,* Adrian Lim,† Steven Moser,† Sohail Ahmad,* Abraham George,* Gowrie Balasubramaniam,* Elaine J. Clutterbuck,* Wladyslaw Gedroyc,† and Edwina A. Brown*

*Clin J Am Soc Nephrol* 3: 1702–1710, 2008

*Table 1.* CT scan scoring parameters

| Peritoneal Calcification | | Peritoneal Thickening | | Bowel Wall Thickening | |
|---|---|---|---|---|---|
| 0 | not identified | 0 | not identified | 0 | not identified |
| 1 | localized area <20% | 1 | localized area <20% | 1 | localized bowel |
| 2 | 20% of peritoneum | 2 | localized <20% | 2 | 20% of bowel |
| 3 | 50% of peritoneum | 3 | 50% of peritoneum | 3 | 50% of bowel |
| 4 | extensive >80% | 4 | extensive >80% | 4 | extensive >80% |
| **Bowel Tethering** | | **Loculation** | | **Bowel Dilatation** | |
| 0 | not present | 0 | not present | 0 | not identified |
| 1 | mild tethering | 1 | <3 locules | 1 | localized bowel |
| 2 | moderate tethering | 2 | 3–6 locules | 2 | 20% of bowel |
| 3 | marked tethering | 3 | multiloculated | 3 | 50% of bowel |
| | | | | 4 | extensive >80% |

Results: Inter-rater agreement was moderate to very good (kappa 0.40 to 0.75) for peritoneal calcification, bowel distribution, bowel wall thickening, and bowel dilation but poorer for loculation of ascites and peritoneal thickening. There was a strongly significant difference between the total CT scan scores at EPS diagnosis and controls (P < 0.00001). Each individual parameter also showed significant differences between EPS and controls (P < 0.006). Bowel tethering and peritoneal calcification were the most specific parameters, and loculation was the least discriminatory parameter. Interestingly, prediagnostic scans a median of 1.5 yr before EPS diagnosis were normal or near-normal in 9 of 13 EPS patients.

Conclusions: CT scanning is a valid and reliable adjunct to the diagnosis of EPS but may not be useful as a screening tool, as the prediagnostic scans did not show abnormalities in many patients who subsequently developed EPS.

Number of patients:
27 EPS + 35 controls

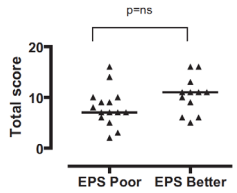



*Figure 3.* Total CT scan scores at diagnosis in EPS patients divided into those with poor final outcome (death or prolonged TPN) and those with better outcome. There was no significant difference in the CT scan scores at diagnosis between the poor and better outcome groups. Horizontal lines indicate median scores.

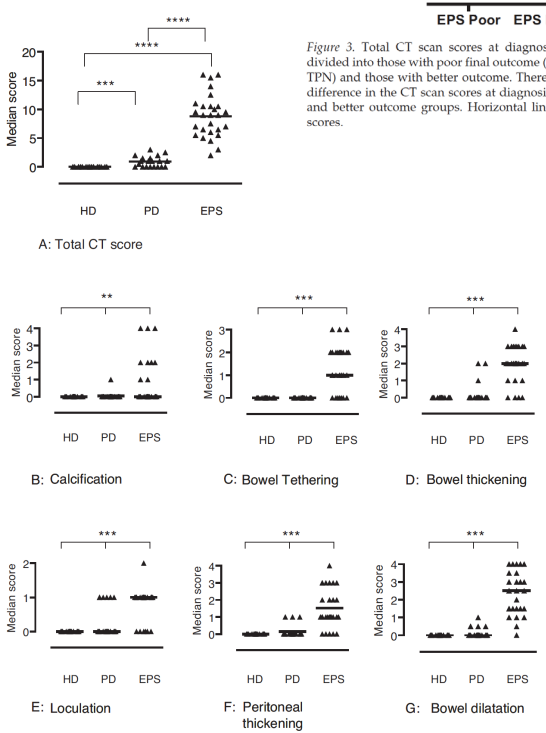



*Figure 2.* CT scan scores for EPS patients, HD and PD controls. (A) Total score (sum of scores for each parameter out of a maximum of 22). (B) Peritoneal calcification. (C) Bowel tethering. (D) Bowel wall thickening. (E) Loculation. (F) Peritoneal thickening. (G) Bowel dilation. $^{**}P < 0.01$, $^{***}P < 0.0001$, $^{****}P < 0.00001$. (A) Wilcoxon rank-sum test. (B–G) Fisher's exact test. Horizontal lines indicate median scores.

*Perit Dial Int* 2009; 29:517–522

# COMPUTED TOMOGRAPHIC FINDINGS CHARACTERISTIC FOR ENCAPSULATING PERITONEAL SCLEROSIS: A CASE-CONTROL STUDY

Anniek Vlijm,[1] Jaap Stoker,[2] Shandra Bipat,[2] Anje M. Spijkerboer,[2] Saffire S.K.S. Phoa,[2]
Robbert Maes,[3] Dirk G. Struijk,[1,4] and Raymond T. Krediet[1]

Results: We included 15 EPS patients and 16 controls. Observer 1 found 6 CT findings that were significantly more often present in EPS than in controls ($p \leq 0.05$): peritoneal enhancement, thickening, and calcifications; adhesions of bowel loops; signs of obstruction; and fluid loculation/septation. Observer 2 scored almost identically but Observer 3 scored differently. The sensitivity and specificity of a combination of specific CT findings were, respectively, 100% and 94% for Observers 1 and 2, and 79% and 88% for Observer 3.

Conclusion: CT scans showed characteristic abnormalities that were significantly more often present in EPS patients compared to long-term PD control patients. CT can be used to confirm the diagnosis of EPS when experienced radiologists apply a combination of specific CT findings.

Computed Tomographic Findings of Encapsulating Peritoneal Sclerosis (EPS) Patients and Controls by the Three Observers

| | Observer 1 | | Observer 2 | | Observer 3 | |
|---|---|---|---|---|---|---|
| | EPS | Controls | EPS | Controls | EPS | Controls |
| Peritoneal enhancement | 10/11[a] | 1/10 | 10/11[a] | 1/10 | 6/10 | 3/10 |
| Peritoneal thickening | 14/15[a] | 3/16 | 14/15[a] | 3/16 | 14/14[b] | 10/16 |
| Peritoneal calcifications | 10/15[b] | 4/16 | 8/15 | 4/16 | 7/14[b] | 2/16 |
| Large bowel wall thickening | 0/15 | 2/16 | 0/15 | 2/16 | 2/12 | 4/16 |
| Small bowel wall thickening | 1/15 | 1/16 | 6/15 | 5/16 | 10/14 | 6/16 |
| Adhesions of bowel loops | 14/15[a] | 0/16 | 14/15[a] | 1/14 | 8/13[b] | 2/16 |
| Signs of bowel obstruction | 6/15[b] | 1/16 | 9/15[c] | 1/16 | 3/14 | 1/16 |
| Fluid loculation/septation | 5/15[b] | 0/16 | 5/15[b] | 0/16 | 2/14 | 1/16 |

The numbers before the slash refer to the number of positive findings, those behind the slash to the number of scans evaluated by each observer. Observer 3 had 14 instead of 15 scans of EPS patients available.
Significant differences are marked:
[a] $p \leq 0.001$.
[b] $p \leq 0.05$.
[c] $p \leq 0.01$.

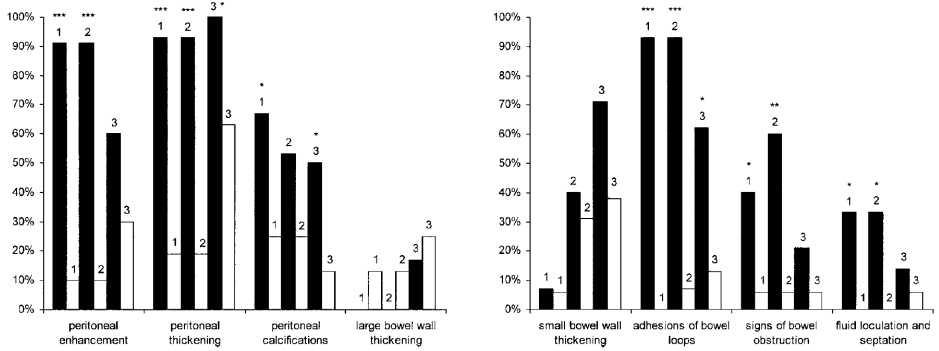



Figure 1 — Computed tomographic findings are represented as percentage of positive findings in EPS patients (black bars) and in controls (white bars). The number above each bar represents the observer (1, 2, or 3). Significant differences between patient groups are marked with asterisks: $*p \leq 0.05$, $**p \leq 0.01$, $***p \leq 0.001$. EPS = encapsulating peritoneal sclerosis.

International Journal of Nephrology and Renovascular Disease 2015:8 83–90

# C-reactive protein levels in combination with abdominal CT scans is a useful tool to predict the macroscopic appearance in late-stage EPS patients prior to surgery

Daniel Kitterer[1]
Stephan Segerer[2]
Wolfgang Steurer[3]
Juergen Dippon[4]
Angela Geissler[5]
Christoph Ulmer[3]
Niko Braun[1]
Mark Dominik Alscher
Joerg Latus[1]

Results: All 30 patients had highly predictive CT scores for EPS. The macroscopic Type III had significantly higher CT scores compared with the other macroscopic phenotypes. Patients with macroscopic Type I had significantly higher C-reactive protein values compared to EPS Type III. Operation time was significantly longer, and repeated surgery and intraoperative complications were more frequent in EPS Type I compared with EPS Type III ($P$<0.05). Using the CT score and CRP level, the sensitivities for prediction of EPS I and III were 78% and 87% with corresponding specificities of 67% and 93%.

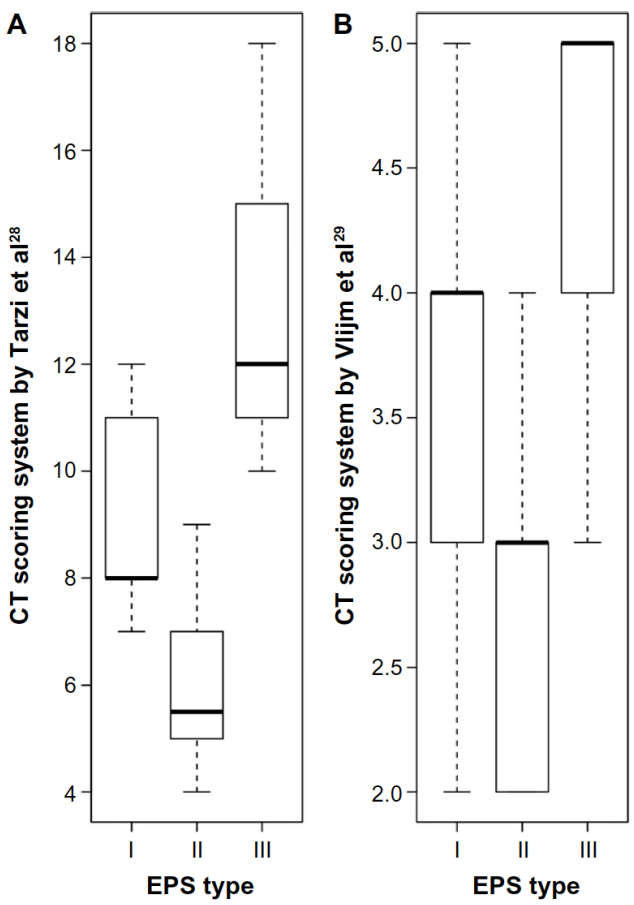



**Figure 2** CT score of patients with different macroscopic phenotypes (mean ± SD) and CRP levels (median with IQR) in patients with EPS Type I–III.
**Notes:** Using the CT scoring system by Tarzi et al[28] (**A**); and the CT scoring system by Vlijm et al[29] (**B**).
**Abbreviations:** CT, computed tomography; SD, standard deviation; CRP, C-reactive protein; IQR, interquartile range; EPS, encapsulating peritoneal sclerosis.

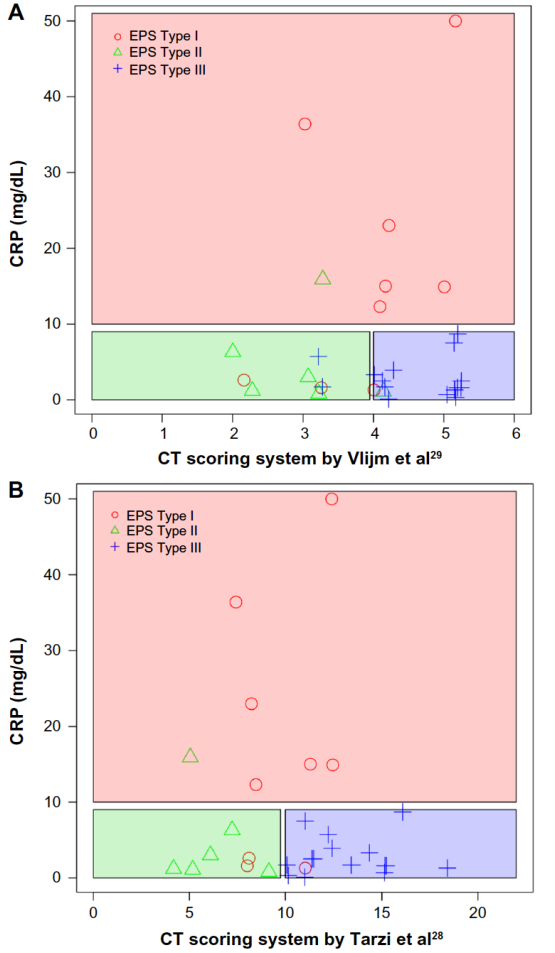



**Figure 3** Prediction of the macroscopic phenotype based on the CT scores
**Notes:** Using the CT scoring system by Vlijm et al[29] (**A**) and the CT scoring system by Tarzi et al[28] (**B**) in combination with CRP values.
**Abbreviations:** CT, computed tomography; CRP, C-reactive protein; EPS, encapsulating peritoneal sclerosis.

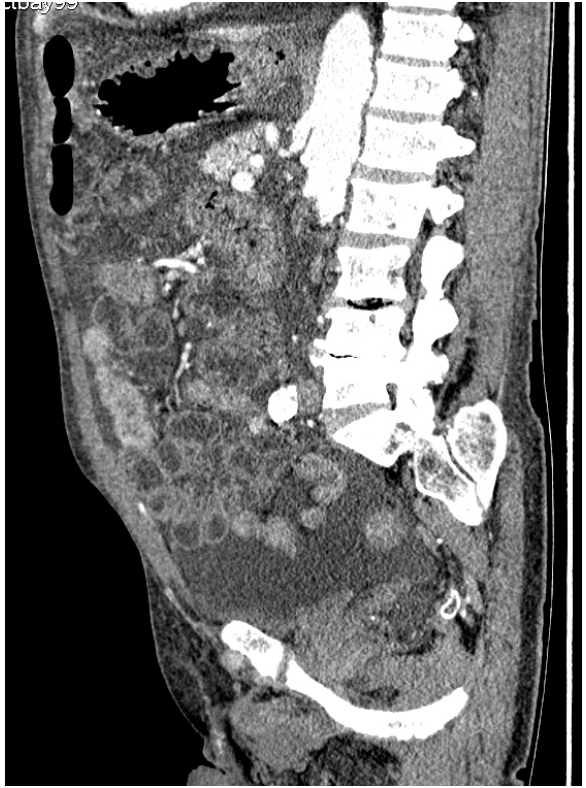
**Accuracy of MDCT in the preoperative definition of Peritoneal Cancer Index (PCI) in patients with advanced ovarian cancer who underwent peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC)** Abdom Imaging (2013) 38:1422–1430

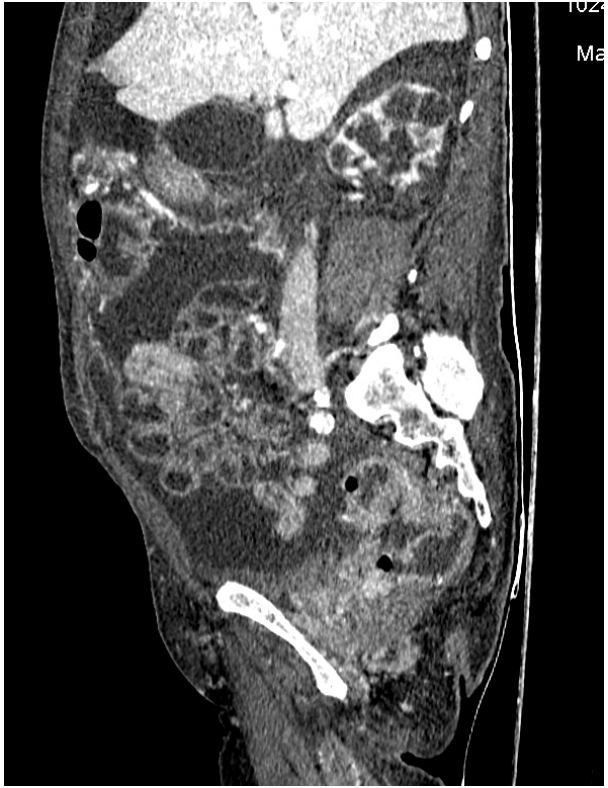
Maria Antonietta Mazzei,[1] Leila Khader,[1] Alfredo Cirigliano,[1] Nevada Cioffi Squitieri,[1]
Susanna Guerrini,[1] Beatrice Forzoni,[1] Daniele Marrelli,[2] Franco Roviello,[2]
Francesco Giuseppe Mazzei,[3] Luca Volterrani[1]

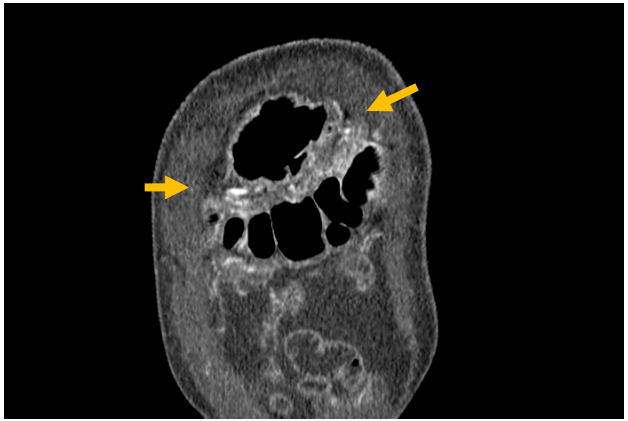
Suggerimenti per la effettuazione di TC per EPS:
- sezioni sottili
- alta energia
- distensione ileale con macrogol (1 litro)
- addome pieno

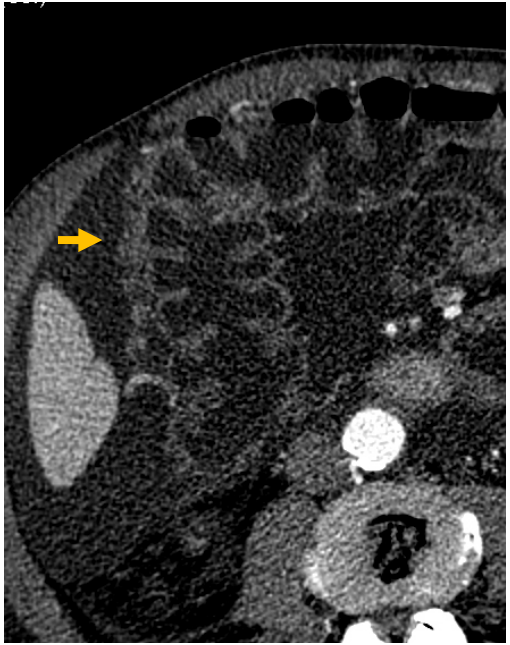
*Conclusion:* Our results encourage the use of MDCT as the only technique sufficient to select patients with peritoneal carcinomatosis for cytoreductive surgery and HIPEC on the condition that a CT examination will be performed using a dedicated protocol optimized to detect minimal peritoneal disease and CT images will be analyzed by an experienced reader.

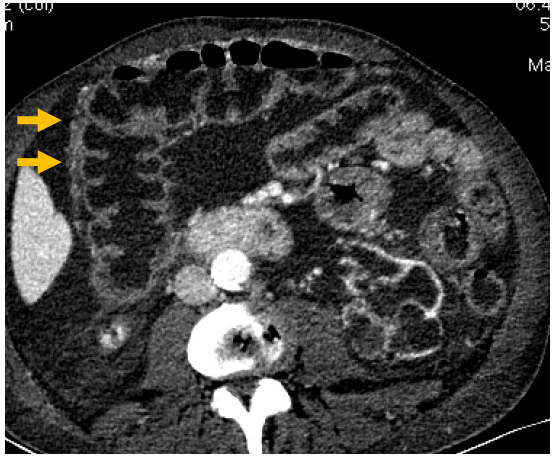
All the CT examinations were performed using unenhanced and contrast-enhanced CT, in the late arterial phase (start delay 45–50 s) and in the portal venous phase (start delay 70–80 s) with an intravenous injection of 2 mL/kg of non-ionic contrast material (Iopamiro 370; Bracco Diagnostics, Milan, Italy), followed by 40 mL of saline solution using a peristaltic semiautomated power injector (4–5 mL/s flow rate, SIAS 757, Bologna Italy) with an 18-gauge needle in the antecubital vein. In 7 patients the bowel distension was obtained through the administration of neutral oral contrast medium (water plus Macrogol [PEG], SELG-ESSE 1000, Promefarm, Milan, Italy). The following technical parameters were used: in 4-row CT, effective slice thickness of 3.75 mm for both plain and contrast-enhanced acquisition CT, beam pitch of 0.75, reconstruction interval of 1.5 mm; tube voltage of 120–140 kVp and reference mAs of 200–320 mAs, in 16-row CT, effective slice thickness of 3.75 mm for plain acquisition and 2.5 mm in contrast-enhanced CT, beam pitch of 1.375/0.937, reconstruction interval of 0.8 mm; tube voltage of 120–140 kVp and reference milliampere seconds of 250–500 mAs; in 64-row CT, effective slice thickness of 3.75 mm for plain acquisition, 1.25 mm in the late arterial phase, and 2.5 mm in the portal venous phase; beam pitch of 0.938, reconstruction interval of 0.8 mm, tube voltage of 120–140 kVp, and reference milliampere seconds of 250/700 mA. An automatic current modulation tube was used to minimize radiation exposure. A standard reconstruction algorithm was used. Patients were instructed not to breath during helical imaging to avoid motion artefacts.

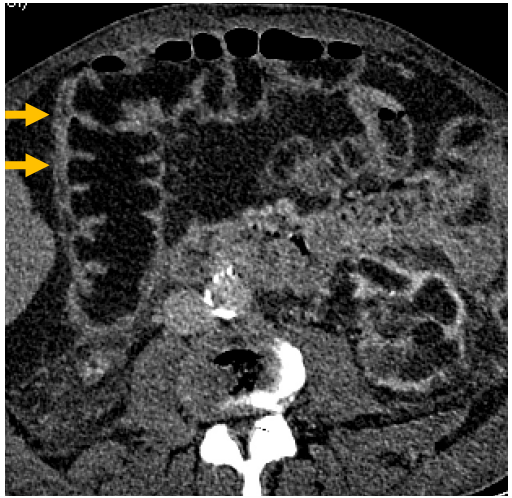


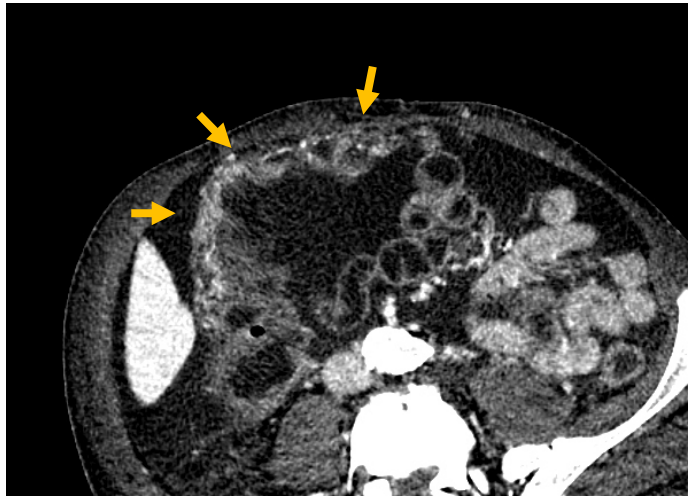


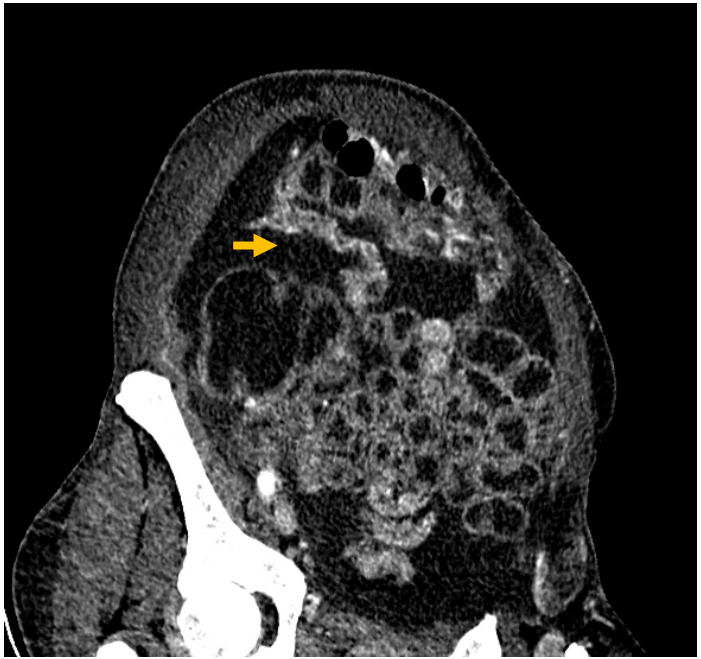


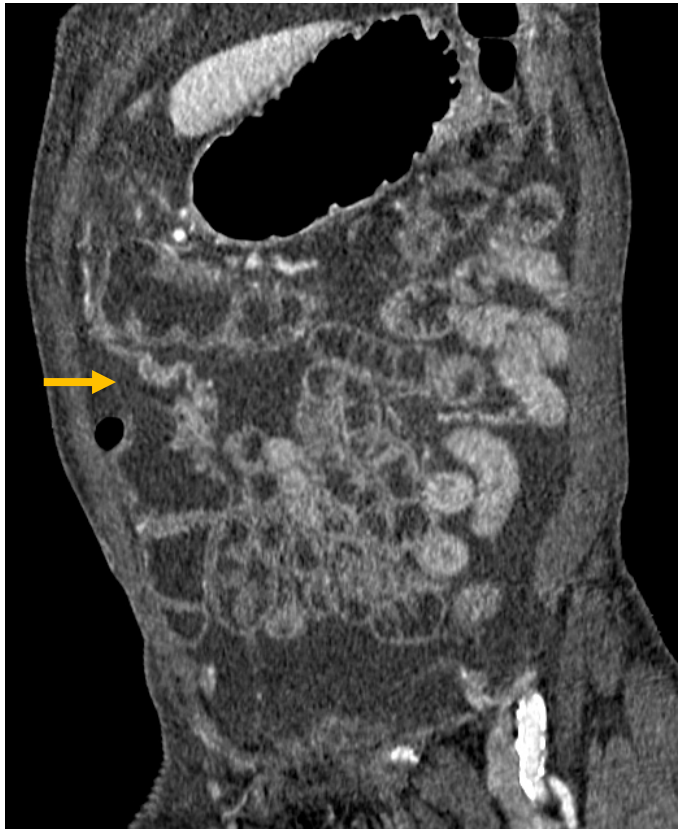












*Perit Dial Int* 2019; 39(5):455–464

# DIRECT COMPARISON OF THE THICKNESS OF THE PARIETAL PERITONEUM USING PERITONEAL BIOPSY AND ULTRASONOGRAPHY OF THE ABDOMINAL WALL IN PATIENTS TREATED WITH PERITONEAL DIALYSIS

Alferso C. Abrahams,[1] Amélie Dendooven,[2,3] Jan Willem van der Veer,[1] Rens Wientjes,[4] Raechel J. Toorop,[5] Ronald L.A.W. Bleys,[6] Antoni P.A. Hendrickx,[7] Maarten S. van Leeuwen,[8] Quido G. de Lussanet,[9] Marianne C. Verhaar,[1] Gerard Stapper,[8] and Tri Q. Nguyen[2]

♦ *Methods:* We performed 3 studies: 1) a human biopsy study to compare US measurement of peritoneal thickness with histological examination; 2) a human cadaver study to investigate the effect of removing the peritoneum on US results; and 3) a phantom study in which we used US to measure the thickness of membrane-like structures with a known thickness to investigate the influence of different US settings.

♦ *Results:* The median thickness in biopsies of the peritoneum was 113 μm (interquartile range [IQR] 72 –129 μm), while this was 370 μm (IQR 324 – 458 μm) when measured by US ($p < 0.0001$). The mean difference between the 2 measures was -257 μm (limits of agreement -4.6 and -511 μm). In the cadaver study, removal of the peritoneum did not have an effect on the presence or thickness of the hyperechoic line reported to represent the peritoneum. In the phantom study, results were highly dependent on frequency of the transducer, scan depth, and gain settings.

♦ *Conclusions:* Ultrasonography results differ markedly from histological measurement using peritoneal biopsies. However, the hyperechoic line generated by US represents the interface between 2 neighboring tissues and not a separate morphological structure. Moreover, its thickness is greatly influenced by user-defined US settings.

Figure 1 — In a human cadaver, an area of 5 X 5 cm of parietal peritoneum was removed.

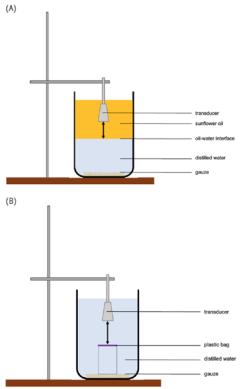



Figure 3 — The experimental set-up to measure the interface between oil and water (A) and to measure the thickness of plastics bags (B).

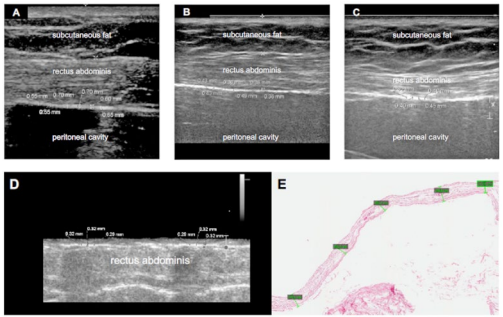



Figure 5 — Ultrasonographic analysis of the abdominal wall of a human cadaver. The mean thickness of the parietal peritoneum measured with the 9-3 MHz transducer was 625 μm (A), while it was 405 μm using the 17-5 MHz transducer (B). After removal of the parietal peritoneum, an intact hyperechoic line was seen with the 17-5 MHz transducer that had a mean thickness of 400 μm (C). When images were made from the inside with the 17-5 MHz transducer on the intact parietal peritoneum, the mean thickness of the hyperechoic line was 310 μm (D, right side), also at the place where the parietal peritoneum was removed (D, on the left side). The mean thickness of the excised parietal peritoneum as assessed by histology was 205 μm (E).

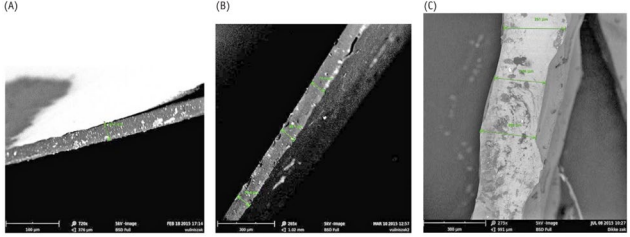



Figure 2 — Scanning electron microscopic images of the 2 plastic bags (A and B) and the peritoneal dialysis drainage bag (C) used for the phantom study.

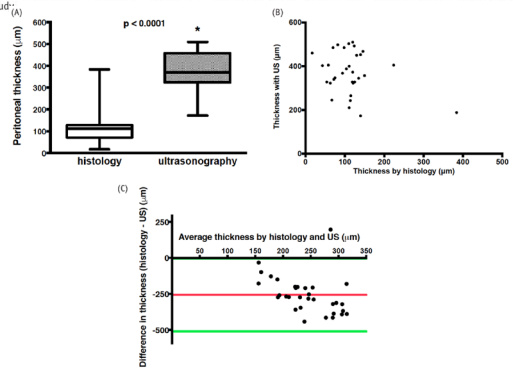



Figure 4 — Box plot showing the thickness of the parietal peritoneum measured in peritoneal biopsies compared with US (A). No correlation was found between the thickness of the parietal peritoneum measured in peritoneal biopsies and by US ($R = -0.09$, $p = 0.61$) (B). Bland-Altman plot of the relation between peritoneal thickness measured in peritoneal biopsies and by US. The mean difference was -257 μm (red line) and the limits of agreement were -4.6 μm and -511 μm (green lines), which indicates that 95% of the difference between these two measurements are within this range (C). US = ultrasonography.

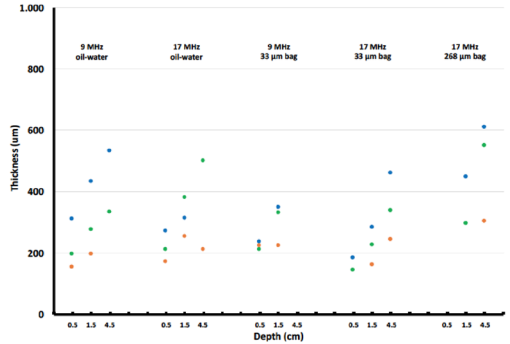



Figure 6 — Thickness measured with ultrasonography of the interface between oil and water, a plastic bag of 33 μm, and a PD drainage bag of 268 μm. Recordings were performed using a 9-3 MHz and 17-5 MHz transducer at 3 different scan depths using 3 different gain setting (blue dot indicates high gain, green dot indicates intermediate gain, and orange dot indicates low gain).

*Perit Dial Int* 2011; 31(3):287-290

# INITIAL OBSERVATIONS USING A NOVEL "CINE" MAGNETIC RESONANCE IMAGING TECHNIQUE TO DETECT CHANGES IN ABDOMINAL MOTION CAUSED BY ENCAPSULATING PERITONEAL SCLEROSIS

Benjamin Wright,[1] Angela Summers,[2] John Fenner,[1] Richard Gillott,[3] Charles E. Hutchinson[2], Paul A. Spencer,[3] Martin Wilkie,[4] Helen Hurst,[2] Sarah Herrick,[5] Paul Brenchley,[2] Titus Augustine,[2] and Karna D. Bardhan[1]

**Encapsulating peritoneal sclerosis (EPS) is an uncommon complication of peritoneal dialysis (PD), with high mortality and morbidity. The peritoneum thickens, dysfunctions, and forms a cocoon that progressively "strangulates" the small intestine, causing malnutrition, ischemia, and infarction. There is as yet no reliable noninvasive means of diagnosis, but recent developments in image analysis of cine magnetic resonance imaging for the recognition of adhesions offers a way forward. We used this protocol before surgery in 3 patients with suspected EPS. Image analysis revealed patterns of abdominal movement that were markedly different from the patterns in healthy volunteers. The volunteers showed marked movement throughout the abdomen; in contrast, movement in EPS patients was restricted to just below the diaphragm. This clear difference provides early "proof of principle" of the approach that we have developed.**

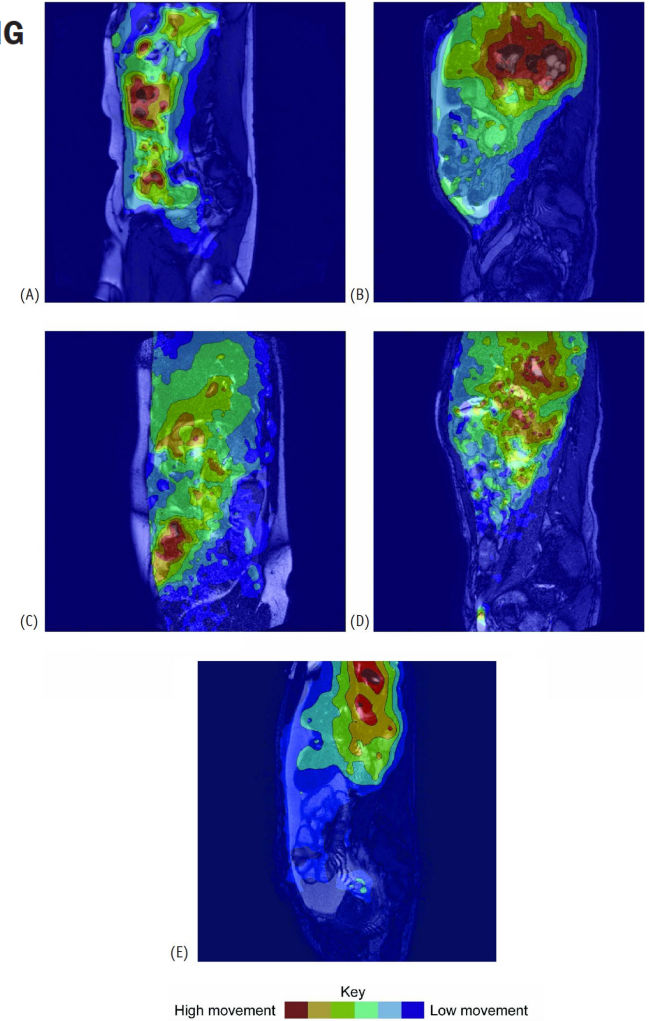



Figure 1 — Healthy volunteers: (A) dataset 1 and (B) dataset 3. Encapsulating peritoneal sclerosis: (C) patient 1, dataset 2; (D) patient 2, dataset 4; (E) patient 3, dataset 5. Details provided in text.

*Perit Dial Int* 2006; 26:224–230

# FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY DETECTS THE INFLAMMATORY PHASE OF SCLEROSING PERITONITIS

Ruth M. Tarzi,[1] John W. Frank,[2] Sohail Ahmad,[1] Jeremy B. Levy,[1] and Edwina A. Brown[1]

♦ *Objective:* We studied the effectiveness of $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) in detecting inflammation in known or suspected cases of sclerosing peritonitis in patients on peritoneal dialysis (PD).

♦ *Design:* We undertook FDG-PET scanning in PD patients presenting with symptoms or signs suggestive of sclerosing peritonitis (SP), and in patients on long-term PD with no symptoms of SP.

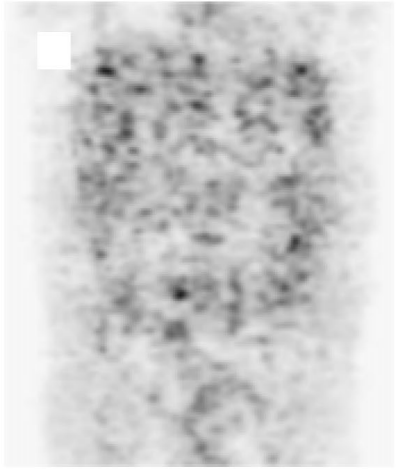
♦ *Setting:* The study was performed in a PD unit in a tertiary-care hospital.

♦ *Patients and Methods:* Three patients with known or strongly suspected SP underwent FDG-PET scans, 1 within 3 months of presentation with symptoms and 2 who were scanned more than 9 months after presentation. One patient was scanned at an early and a late time point. Five patients who had been on PD for more than 5 years and who were asymptomatic also underwent FDG-PET scanning. Scans were interpreted by a specialist in nuclear medicine.

♦ *Results:* The scan performed in the early stages of SP showed increased peritoneal uptake. However, three scans taken more than 9 months after presentation with suspected SP showed mild peritoneal abnormalities only. One of 5 asymptomatic long-term PD patients showed increased peritoneal uptake associated with loss of ultrafiltration and high transporter status.

♦ *Conclusions:* FDG-PET scanning may be a useful adjunct in the diagnosis of the acute phase of SP. More study is needed to define its role in the diagnosis of SP in asymptomatic PD patients.

A



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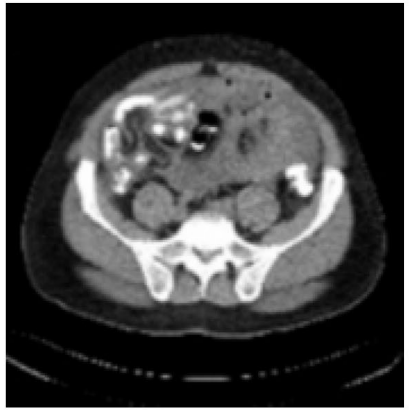

Figure 4 — Coronal FDG-PET scan of Patient 4 shows diffusely increased peritoneal uptake, with focal areas of higher uptake within the peritoneum (A). Contrast-enhanced computed tomography of the abdomen of Patient 4 taken around the same time as the FDG-PET scan shows no gross peritoneal changes (B).

# EPS: diagnosi

clinica

TC (scarso valore altre metodiche di imaging)

→ anatomia patologica

# Histological Criteria for Encapsulating Peritoneal Sclerosis – A Standardized Approach

Niko Braun[1], Peter Fritz[2], Christoph Ulmer[3], Joerg Latus[1]*, Martin Kimmel[1], Dagmar Biegger[2], German Ott[4], Fabian Reimold[1,5], Klaus-Peter Thon[3], Juergen Dippon[6], Stephan Segerer[7], M. Dominik Alscher[1]

PLOS ONE November 2012 | Volume 7 | Issue 11 | e48647

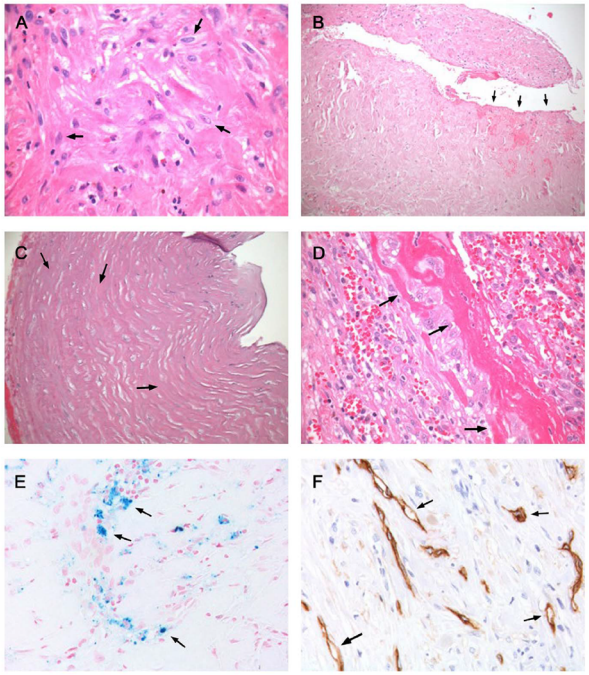


**Figure 1. Histopathological findings in EPS compared to simple sclerosis. A** HE staining showing an increased cellularity, round cells and fibroblast like cells (arrows). EPS, original magnification ×40; **B** HE staining showing a decreased cellularity, fibrin deposits and a complete denudation of the mesothelial cell layer with fibrin exudations (arrows). EPS, original magnification ×100; **C** HE staining showing a decreased cellularity with intracellular matrix (arrows), complete mesothelial denudation with fibrin exudations. EPS, original magnification ×200; **D** HE staining showing an increased cellularity, hemorrhage, round cells, fibroblast like cells and fibrin deposits (arrows). EPS, original magnification ×400; **E** Fe staining showing vessels, intraluminal erythrocytes and Fe deposits (arrows). EPS, original magnification ×400; **F** D2–40 stained section showing podoplanin positive cells associated to vessels (arrows). EPS, original magnification ×400.

Number of cases: 31 EPS + 27 PD controls

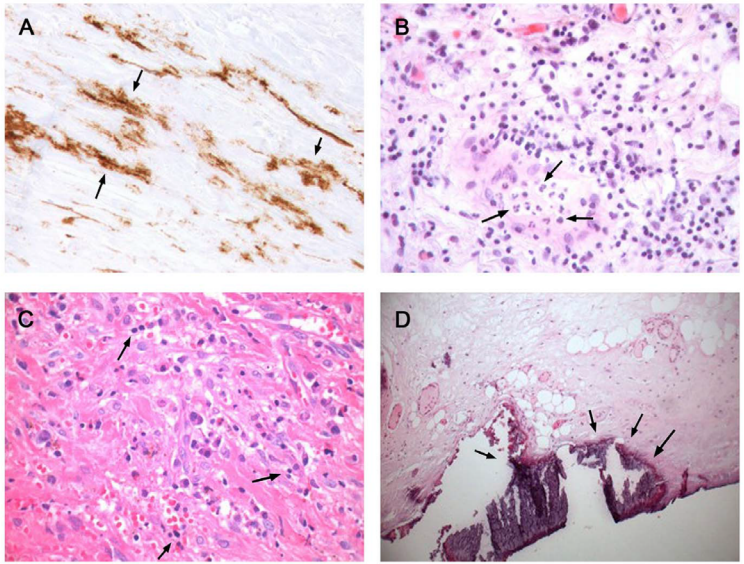


**Figure 2. Histopathological findings in EPS compared to simple sclerosis. A** D2–40 stained section showing podoplanin positive cells not associated to vessels (arrows). EPS, original magnification ×400; **B** HE staining showing acute and chronic inflammation with round cells and neutrophils (arrows). EPS, original magnification ×400; **C** HE staining showing fibroblast like cells, eosinophils, plasma cells and round cells (arrows). EPS, original magnification ×400; **D** HE staining showing vasculitis, round cells and calcium deposits (arrows). EPS, original magnification ×100.

Results: The following findings were significantly more common in EPS than in patients on PD without EPS: fibroblast like cells (FLC) ($p<0.0001$), mesothelial denudation ($p<0.0001$), decreased cellularity ($p = 0.008$), fibrin deposits ($p<0.03$), Fe deposits ($p = 0.05$), podoplanin vascular ($p < 0.0001$), podoplanin avascular ($p < 0.0001$). Using all predictor variables we trained the classification method Random Forest to categorize future cases. Podoplanin vascular and avascular were taken together ($p <0.0001$), FLC ($p <0.0001$), mesothelial denudation ($p = 0.0005$), calcification ($p = 0.0026$), acellular areas ($p = 0.0094$), and fibrin deposits ($p = 0.0336$) showed up as significantly important predictor variables. Estimated misclassification error rate when classifying new cases turned out to be 14%.

# Strategie e terapie contro danno di membrana e EPS

"data di scadenza" per la PD: un concetto errato (e pericoloso)

valutazione membrane disfunction, sodium sieving, sodium dip

utilizzo soluzioni biocompatibili

prevenzione e terapia accurate delle peritoniti

ipertensione: si ACE-I o ARB; attenzione ai β-bloccanti

possibile profilassi con tamoxifene nei casi a rischio

trapianto dopo PD: alto rischio con CNI in assenza di mTOR-I

# Strategie e terapie contro danno di membrana e EPS

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nephron Clinical Practice

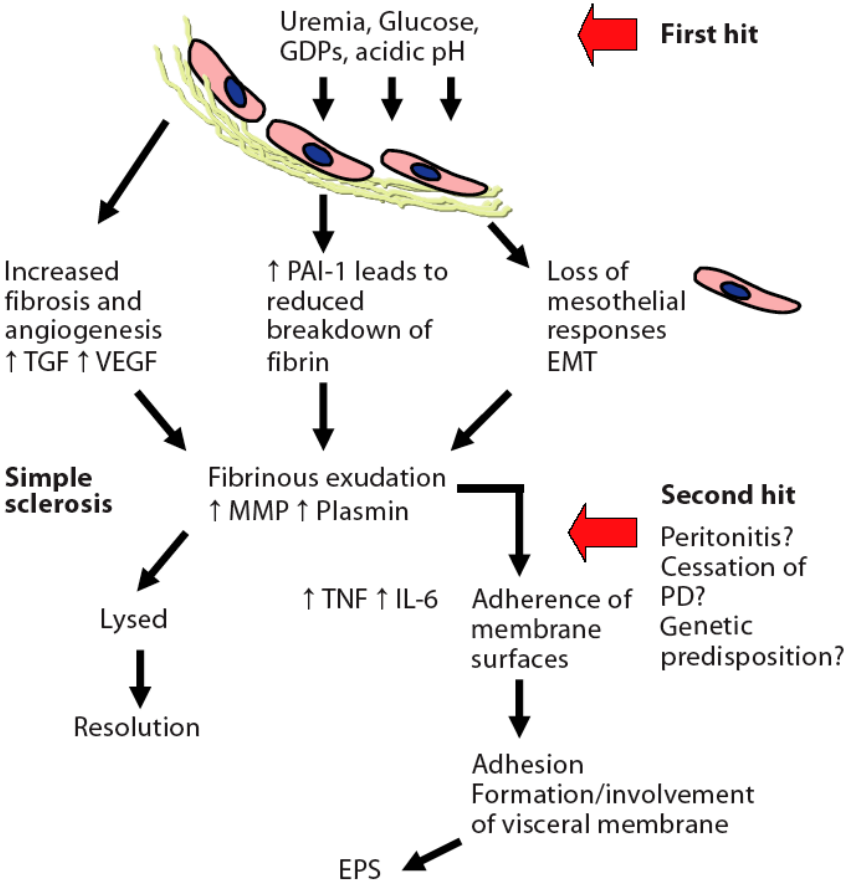
Nephron Clin Pract 2009;111:c149–c154
DOI: 10.1159/000191214

# Encapsulating Peritoneal Sclerosis: Clinical Significance and Implications

T. Augustine[a] P.W. Brown[b] S.D. Davies[d] A.M. Summers[a] M.E. Wilkie[c]

[a]Manchester Institute of Nephrology and Transplantation, Manchester Royal Infirmary, Manchester, [b]Department of Diagnostic Imaging and [c]Sheffield Kidney Institute, Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, and [d]Department of Nephrology, University Hospital of North Staffordshire, Stoke-on-Trent, UK

**two-hit hypothesis**



**ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention**

Peritoneal Dialysis International
2021, Vol. 41(4) 352–372

Johann Morelle[1], Joanna Stachowska-Pietka[2], Carl Öberg[3], Liliana Gadola[4], Vincenzo La Milia[5], Zanzhe Yu[6], Mark Lambie[7], Rajnish Mehrotra[8], Javier de Arteaga[9] and Simon Davies[7]

The pathology of EPS is different to progressive membrane fibrosis which does not inevitably progress to EPS and it should be emphasized that length of time on treatment remains the strongest risk factor. It is also important to take competing risks of death into account when assessing EPS risk, as older, more comorbid individuals are far more likely to die from non-EPS causes.

*Peritoneal Dialysis International*, Vol. 37, pp. 362–374
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**ISPD GUIDELINES/RECOMMENDATIONS**

# LENGTH OF TIME ON PERITONEAL DIALYSIS AND ENCAPSULATING PERITONEAL SCLEROSIS — POSITION PAPER FOR ISPD: 2017 UPDATE

Edwina A. Brown,[1] Joanne Bargman,[2] Wim van Biesen,[3] Ming-Yang Chang,[4] Frederic O. Finkelstein,[5] Helen Hurst,[6] David W. Johnson,[7] Hideki Kawanishi,[8] Mark Lambie,[9] Thyago Proença de Moraes,[10] Johann Morelle,[11] and Graham Woodrow[12]

Encapsulating peritoneal sclerosis is a rare condition. There is no evidence to withhold PD as a treatment option because of fear of development of EPS. There is insufficient evidence to support a single rule about optimal length of time on PD to avoid the risk of EPS.

Each long-term patient needs to be considered individually, taking into account the following factors:

1. Age and prognosis of patient;
2. Length of time on PD;
3. Quality of PD (dialysis adequacy, ultrafiltration, peritonitis frequency);
4. Access to and suitability for transplantation;
5. Potential risk of HD in the particular patient (hemodynamic stability, vascular access);
6. Quality of life of the patient.

All these items should be discussed and any decision arrived at by shared decision-making.

Int Urol Nephrol (2009) 41:903–907
DOI 10.1007/s11255-009-9661-7

NEPHROLOGY - EDITORIAL

# No need for an "expiry date" in chronic peritoneal dialysis to prevent encapsulating peritoneal sclerosis

Guido Garosi · Dimitrios G. Oreopoulos

The idea of an "expiry date for PD", that is spreading among nephrologists, especially in developed countries, has no rational basis and may be potentially harmful to the patient who is forced to change to hemodialysis after a fixed time on PD in the absence of definite indications. Furthermore the risks of such a transfer, especially with a tunnelled line could equal or even surpass the risk of ever getting EPS and also could impact negatively on the patient's quality of life.

# Strategie e terapie contro danno di membrana e EPS

"data di scadenza" per la PD: un concetto errato (e pericoloso)

➡ valutazione membrane disfunction, sodium sieving, sodium dip

utilizzo soluzioni biocompatibili

prevenzione e terapia accurate delle peritoniti

ipertensione: si ACE-I o ARB; attenzione ai β-bloccanti

possibile profilassi con tamoxifene nei casi a rischio

trapianto dopo PD: alto rischio con CNI in assenza di mTOR-I

**ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention**

Peritoneal Dialysis International
2021, Vol. 41(4) 352–372

Johann Morelle[1], Joanna Stachowska-Pietka[2], Carl Öberg[3], Liliana Gadola[4], Vincenzo La Milia[5], Zanzhe Yu[6], Mark Lambie[7], Rajnish Mehrotra[8], Javier de Arteaga[9] and Simon Davies[7]

Guideline 3: Recognizing low UF capacity: This is easy to measure and a valuable screening test. Insufficient UF should be suspected when either (a) the net UF from a 4-h PET is <400 ml (3.86% glucose/4.25% dextrose) or <100 ml (2.27% glucose /2.5% dextrose), (GRADE 1) and/or (b) the daily UF is insufficient to maintain adequate fluid status. (practice point) Besides membrane dysfunction, low UF capacity can also result from mechanical problems, leaks or increased fluid absorption across the peritoneal membrane not explained by fast PSTR.

Guideline 4a: Diagnosing intrinsic membrane dysfunction (manifesting as low osmotic conductance to glucose) as a cause of UF insufficiency: When insufficient UF is suspected, the 4-h PET should be supplemented by measurement of the sodium dip at 1 h using a 3.86% glucose/4.25% dextrose exchange for diagnostic purposes. A sodium dip 5 mmol/L and/or a sodium sieving ratio 0.03 at 1 h indicates UF insufficiency. (GRADE 2B)

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**Table 1.** Classification of membrane dysfunction, including definition, underlying pathophysiology and clinical implications.

| Classification | Definition | Pathophysiology | Clinical implications and actions |
|---|---|---|---|
| Fast PSTR | D/P creatinine ratio above the population mean value at the end of a 4-h PET using either 2.27/2.5% or 3.86/4.25% glucose/dextrose-based solution. While most studies report that PSTR is normally distributed, with a typical average value of 0.65, multicentre studies show a significant centre effect.<br>It can be present at the start of PD and/or develop or resolve over time | • Membrane inflammation causing a large effective vascular surface area<br>• Neovascularization<br>• Both the above may potentially be, in part, genetically determined | • Reduces net ultrafiltration with glucose-based dialysate due to early loss of the osmotic gradient and more rapid fluid reabsorption<br>• In patients with significant residual kidney function, 'dry' nights when treated with CAPD or partial or complete 'dry' days when treated with APD. If long dwells required use icodextrin (daytime for APD, overnight for CAPD)<br>• Shorten glucose-based overnight dwells (e.g. 90–180 min) when using APD coupled with icodextrin during the day long dwell.<br>• If neither APD nor icodextrin available increase glucose strength to prevent reabsorption. |
| Poor intrinsic ultrafiltration (low OCG at start of PD | Sodium dip at 60 min $\leq$5 mmol/l or sodium sieving ratio <0.07 with a 3.86% glucose/4.25% dextrose PET | • Explanations largely not understood<br>• Potential influence of genetic determinants (e.g. aquaporin expression)<br>• Note: a low $\Delta D_{Na}$ 0–60 min can also be observed in patients with very fast PSTR due to early dissipation of the osmotic gradient | • Low OCG at baseline: careful evaluation and monitoring of fluid volume.<br>• May be associated with fast PSTR<br>• Earlier indicator of ultrafiltration insufficiency than fast PSTR |
| Acquired intrinsic ultrafiltration insufficiency (low OCG) developing over time (years) on PD | Sodium dip at 60 min $\leq$5 mmol/L or sodium sieving ratio <0.07 with a 3.86% glucose /4.25% dextrose PET | • Structural alterations in the peritoneal interstitium in keeping with progressive fibrosis<br>• Usually associated with fast PSTR | • Discussion about the potential risks of continuing PD, including EPS, vs. transition to another modality, and shared decision-making with the patient and the PD team |

PSTR: peritoneal solute transfer rate; D/P: dialysate to plasma; PET: peritoneal equilibration test; PD: peritoneal dialysis; CAPD: continuous ambulatory peritoneal dialysis; APD: automated peritoneal dialysis; OCG: osmotic conductance to glucose; EPS: encapsulating peritoneal sclerosis.

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A progressive and excessive decline in OCG (e.g. loss of sodium sieving or sodium dip) might be used as an independent predictor for the risk of EPS.

The sodium dip is effectively lost in the presence of severe UF insufficiency and a progressive decline in the sodium dip over some years is a better discriminator for subsequent UF failure than the longitudinal change in PSTR. In several studies, the progressive reduction in the sodium dip was also a better discriminator of those patients who were more likely to go on to develop EPS. These studies identified a sodium dip 5 mmol/L or a sodium sieving ratio of <0.03 as high risk for EPS.

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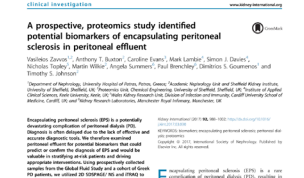
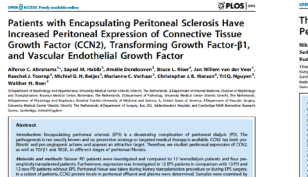
A number of candidate biomarkers have been identified but to date these are not sufficiently discriminatory to inform clinical decision-making. Reliable biomarkers will require external validation and the development of reliable prognostic models.

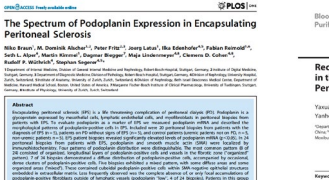

ORIGINAL ARTICLES

EARLY DIAGNOSTIC MARKERS FOR ENCAPSULATING PERITONEAL SCLEROSIS: A CASE-CONTROL STUDY


clinical investigation

A prospective, proteomics study identified potential biomarkers of encapsulating peritoneal sclerosis in peritoneal effluent


Patients with Encapsulating Peritoneal Sclerosis Have Increased Peritoneal Expression of Connective Tissue Growth Factor (CCN2), Transforming Growth Factor-β1, and Vascular Endothelial Growth Factor


The Spectrum of Podoplanin Expression in Encapsulating Peritoneal Sclerosis


Peritoneal Dialysis – Meta-Analysis

Recent Understanding and Future Directions in the Application of MMP-2 in Encapsulating Peritoneal Sclerosis Clinical Practice


Clinica Chimica Acta

Peritoneal effluent MicroRNA profile for detection of encapsulating peritoneal sclerosis

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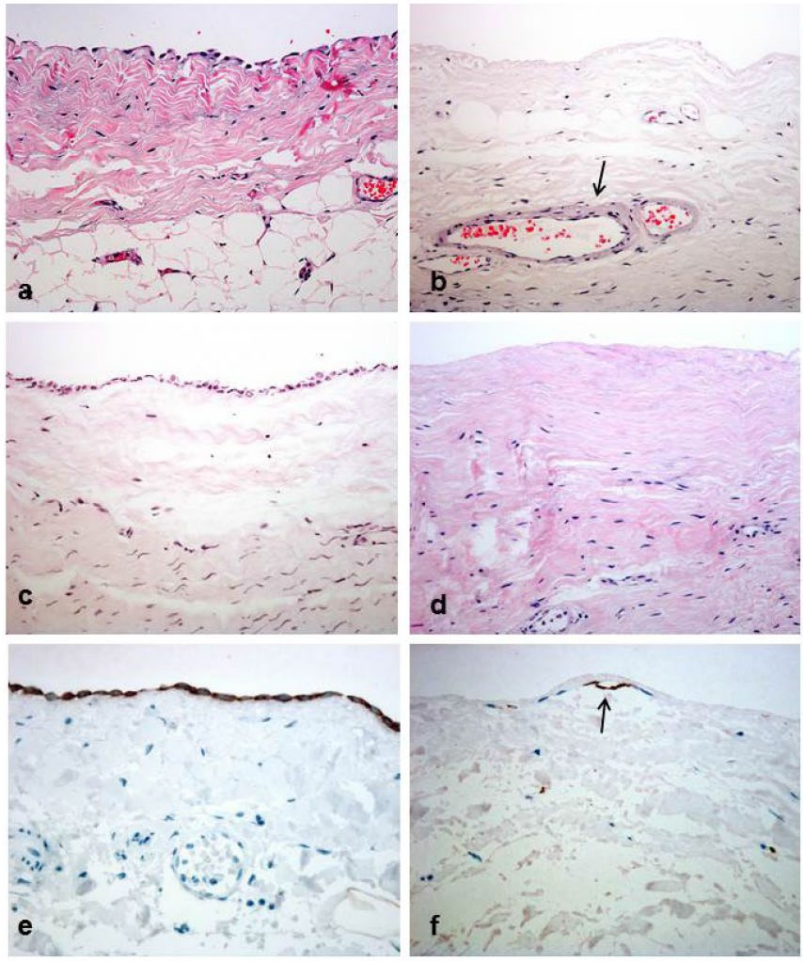
*Perit Dial Int* 2016; 36(2):129–134

# BIOCOMPATIBLE DIALYSIS SOLUTIONS PRESERVE PERITONEAL MESOTHELIAL CELL AND VESSEL WALL INTEGRITY. A CASE-CONTROL STUDY ON HUMAN BIOPSIES

Gloria del Peso,[1] José Antonio Jiménez-Heffernan,[2] Rafael Selgas,[1] César Remón,[3] Marta Ossorio,[1] Antonio Fernández-Perpén,[4] José Antonio Sánchez-Tomero,[4] Antonio Cirugeda,[5] Erika de Sousa,[1] Pilar Sandoval,[6] Raquel Díaz,[1] Manuel López-Cabrera,[6] and María Auxiliadora Bajo[1]

*Patients:* 23 + 23

*Results:* A total of 56.5% of SG patients showed total or partial preservation of mesothelial cells monolayer, in contrast with 26.1% of patients in CG ($p = 0.036$). Peritoneal fibrosis was not significantly less frequent in SG patients (47.8% SG vs 69.6% CG; $p = 0.13$). In patients without previous peritonitis, a significantly lower prevalence of fibrosis was present in SG patients (41.7% SG vs 77.8% CG; $p = 0.04$). Hyalinizing vasculopathy (HV) was significantly lower in SG (4.3% SG vs 30.4% CG; $p = 0.02$). Cytokeratin-positive fibroblast-like cells were detected in 10 patients (22%), but the prevalence was not significantly lower in SG. In the univariate regression analysis, the use of biocompatible solutions was associated with mesothelial monolayer integrity ($p = 0.04$) and an absence of vasculopathy ($p=0.04$).



Blood Purif
DOI: 10.1159/000510282 Published online: February 10, 2021

# Recent Understanding of Peritoneal Pathology in Peritoneal Dialysis Patients in Japan

Chieko Hamada[a] Yasuhiko Tomino[b]

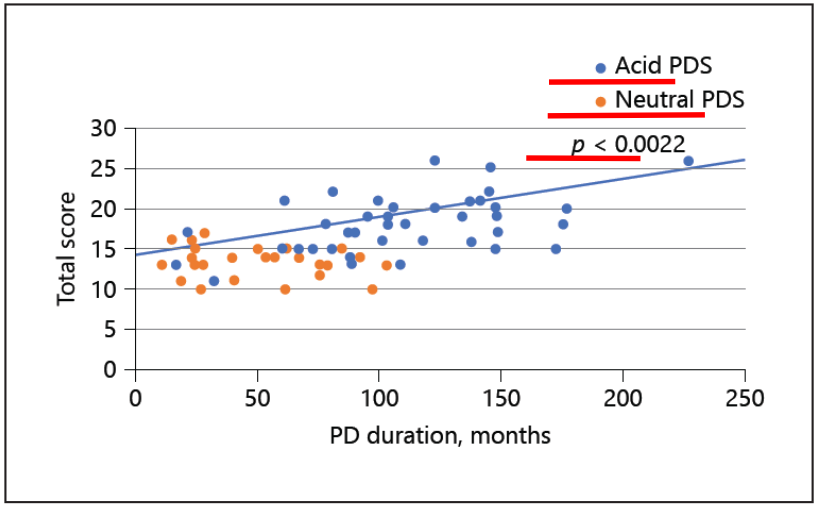
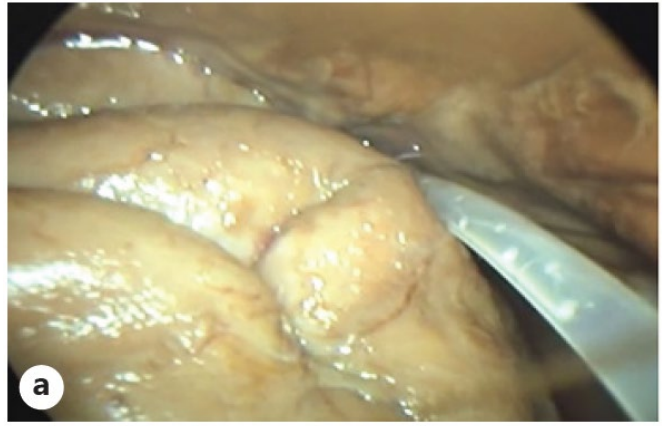
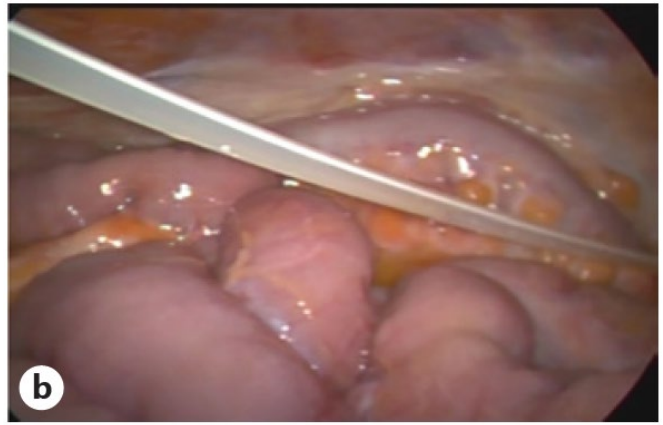




**Fig. 4.** Macroscopic morphological alterations in the peritoneum of patients undergoing PD. Blue circles indicate acidic dialysate group, and red circles indicate neutral dialysis group. Changes in the laparoscopic finding scores based on PD duration and the use of acidic and neutral PDS ($p = 0.0022$ in acidic PDS). PD, peritoneal dialysis; PDS, peritoneal dialysis solution.




Case treated with acidic PDS




Case treated with neutral PDS

Clinical and Experimental Nephrology (2023) 27:717–727

# Pathophysiology of encapsulating peritoneal sclerosis: lessons from findings of the past three decades in Japan

Masaaki Nakayama[1] · Masanobu Miyazaki[2] · Chieko Hamada[3] · Yasuhiko Ito[4] · Kazuho Honda[5] · Peritoneal Biopsy Study Group of the Japanese Society for Peritoneal Dialysis

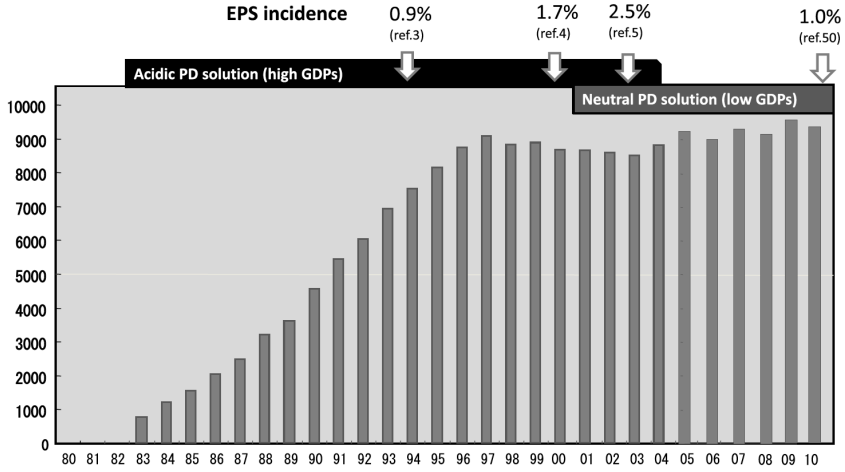



**Fig. 1** Number of peritoneal dialysis (PD) patients and incidence of encapsulating peritoneal sclerosis (EPS) in Japan. The Working Group on Sclerosing Encapsulating Peritonitis (SEP) of the Ministry of Health, Labour and Welfare of Japan, issued a draft clinical guide for the diagnosis and management of SEP in 1998 [56]. Thereafter, an ad hoc committee of the International Society of Peritoneal Dialysis (ISPD) published a position statement on the diagnosis and management of EPS in 2000 [2], and a Japanese working group issued a proposal for the diagnosis and treatment of EPS in 2005 [57]. The Japanese Society for Dialysis Therapy (JSDT) issued a guideline for preventing EPS in 2009 [58], which recommended a planned PD withdrawal in those patients on long-term PD therapy who present a persistent high transport state

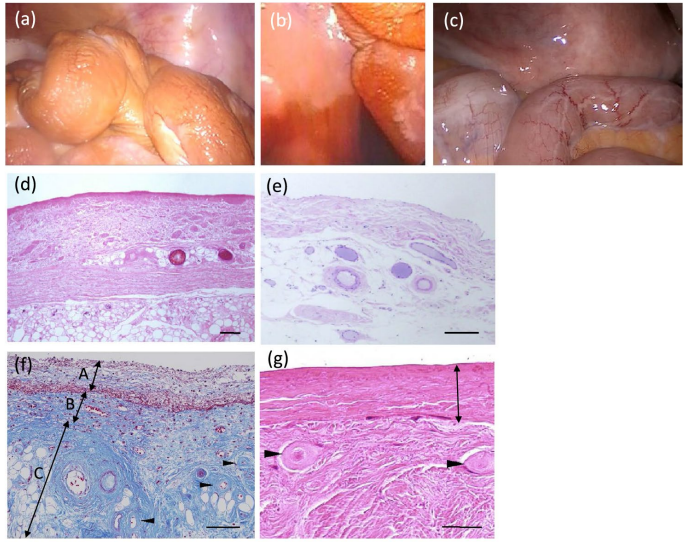



**Fig. 5** Representative macroscopic and microscopic pathology of the peritoneum undergoing long-term peritoneal dialysis (PD). Macroscopic findings by laparoscopy in a case undergoing PD for 12-years using conventional acidic PD solution (**a**), 6-years using acidic PD solution (**b**), or for 5.5-years using neutral PD solution (**c**). Histology of the peritoneum of the patient undergoing PD more than 10-years using conventional PD solution (**d**–**g**), or neutral PD solution (**e**) [**d**, **e**, **g** Hematoxylin and eosin stain, **f** Masson trichrome stain, **d**–**f** scale bar 100 μm, **g** scale bar 50 μm]. The image (**d**) shows a thickened compact zone with hyalinosis, complete loss of the mesothelial layer, fibrin exudates on the peritoneal surface, and a thickened vascular wall accompanied by luminal obstruction. The image (**e**) shows a preserved mesothelial layer and mild fibrosis of the compact zone without hyalinous degeneration of collagen fibers. No vascular wall thickening or obstruction are seen. The image (**e**) shows double-layered neo-membrane covering the proper peritoneum of omentum (autopsy). Superficial neo-membrane (A) contains fresh fibrin exudates and inflammatory cells due to accompanying peritonitis. Deeper neo-membrane (B) contains organization of fibrin exudates with microvascular proliferation. Proper peritoneum (C) shows fibrosis and hyalinizing vasculopathy of the post-capillary venules with luminal narrowing or obliteration (arrow heads). The image (**g**) shows neo-membrane (arrow) covering the surface of proper parietal peritoneum with extensive fibrosis and obstructive vasculopathy (arrow heads). Image (**e**) was kindly provided by Dr. Ishibashi of The University of Tokyo/Japanese Red Cross Medical Center

Based on the clinical experiences in Japan, conventional acidic PD solutions were hypothesized to be primary drivers of peritoneal membrane damage in patients undergoing PD therapy. The presence of GDPs in such PD solutions, and the associated production of AGEs in the peritoneal membrane, are thought to play a major role in the etiology of peritoneal damage (PS) in such cases. Empirical results, epidemiology, and histological analysis all indicate that low-GDP neutral PD solutions help to preserve peritoneal membrane integrity during PD, thereby lessening the risk of development of EPS.

For cases treated using a neutral PD solution, the induction of peritoneal damage by the PD solution appears to have been lessened.

Instead, peritonitis is now considered a risk factor for EPS.

One hypothesis has been considered that EPS represents a more severe form of PS. However, laparoscopic and histological findings suggested the need for a paradigm change regarding the pathophysiology of EPS. We conjecture that EPS is not, in fact, a form of PS, but is, instead a physiological wound-healing reaction to peritoneal injury.

Blood Purif Published online: August 25, 2022

# Histopathological Changes of Long-Term Peritoneal Dialysis Using Physiological Solutions: A Case Report and Review of the Literature

Guido Filler[a, b, c, d] Aaron Haig[c] Neil Merritt[e] Ana Catalina Alvarez-Elias[f, g]
Chia Wei Teoh[f] Timm Joachim Filler[h] Maria Esther Díaz-González de Ferris[i]

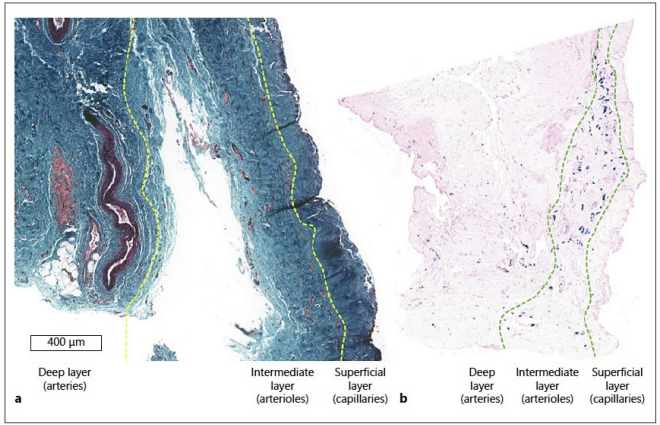



**Fig. 3.** On the left (**a**): trichrome stain of peritoneal biopsy showing fibrosis and thickening of the peritoneum, but specific findings of EPS were absent (mesothelial cells were intact, lack of fibrin exudation, no increase in infiltration or calcification, no neomembrane or fibroblast proliferation). On the right (**b**): histological image showing extensive hemosiderin deposition.

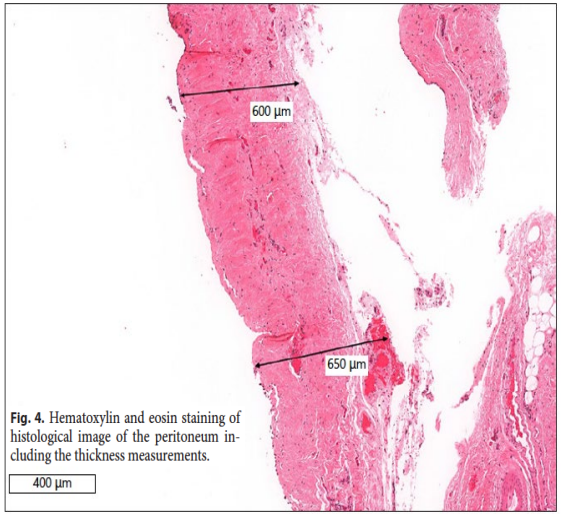




**Fig. 4.** Hematoxylin and eosin staining of histological image of the peritoneum including the thickness measurements.

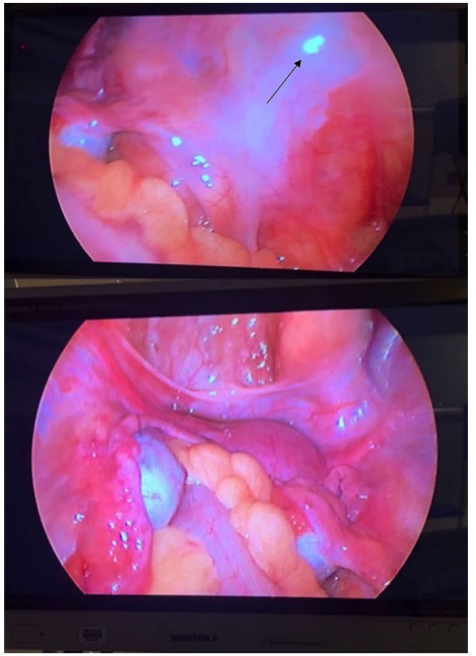


**Fig. 2.** Laparoscopic image of the visceral peritoneum appearing mostly normal. However, there was one area of lateral peritoneal wall showing a glistening white plaque and presumed sclerosis.

## Conclusions:

While the biopsy was reassuring with respect to the absence of EPS, significant histopathological changes suggest that avoiding pH trauma may not ameliorate the effects of glucose exposure in long-term PD.

Peritoneal Dialysis International 2021 DOI: 10.1177/08968608211027008

# Do low GDP neutral pH solutions prevent or retard peritoneal membrane alterations in long-term peritoneal dialysis?

Alena Parikova[1], Kristyna Michalickova[1], Anouk TN van Diepen[2], Luděk Voska[3], Ondrej Viklicky[1] and Raymond T Krediet[4]

It can be concluded that the main advantage of PD with L-GDP/N-pH dialysis solutions may be the reduction and delay of functional and morphologic alterations, but not complete obliteration, that can occur in long-term PD, possibly preventing EPS.

**Table 3.** Morphologic differences between long-term treatment with conventional and low ↑GDP neutral pH dialysis solutions.[a]

| | Conventional | | L-GDP/N-pH | | |
|---|---|---|---|---|---|
| Year[ref] | Number of patients | PD duration (years) | Number of patients | PD duration (years) | Differences |
| 2013[18] | 12 | 5 ± 0.5 | 12 | 4 ± 0.5 | Submesothelial fibrosis ↓<br>Lumen/vessel diameter ↑<br>AGE ↓, but still present |
| 2015[20] | 19 | 0 to >5 | 29 | 0 to >5 | Submesothelial fibrosis =<br>Lumen/vessel diameter ↑ |
| 2016[19] | 23 | 2 ± 1.5 | 23 | 2 ± 1.3 | Mesothelium↑<br>Submesothelial fibrosis↓<br>Vasculopathy↓<br>EMT = |
| 2019[21b] | 54 | 7 (6–11) | 73 | 2–6 | Submesothelial fibrosis ↓[c]<br>Lumen/vessel diameter ↑<br>AGE ↓, but still present |

L-GDP-N-pH: pow GDP neutral pH; EMT: endothelial-to-mesenchymal transition.
[a]Studies are cited according to the year of publication. Means ± SD is given, or medians (range).
[b]Patients from the literature[20] are included.
[c]All differences were also present when only patients with a PD duration from 4 years to 10 years were analyzed separately.

**Table 5.** Longitudinal follow-up studies on peritoneal transport in incident PD patients comparing conventional with low GDP neutral pH dialysis solutions.

| | | | Conventional | | L-GDP/N-pH | | |
|---|---|---|---|---|---|---|---|
| Year[ref] | Single/ multicenter | Test solution (glucose conc) | Number of patients | Follow-up (years) | Number of patients | Follow-up (years) | Key findings with L-GDP/N-pH, compared to conventional |
| 2012[35] | Multi/RCT | 2.27% | 82 | 2 | 85 | 2 | Initial $D/P_{creat}$ ↑, ultrafiltration =<br>Follow-up $D/P_{creat}$ =, ultrafiltration = |
| 2018[40] | Multi/long | 2.27% | 295 | Median 3 | 71 | Median 2 | Initial $D/P_{creat}$ ↓, ↑ for 2 years, thereafter =; no ultrafiltration data |
| 2020[41] | Single/long | 3.86% | 135 | Median 2<br>IQR 1-4 | 116 | Median 2<br>IQR 1-6 | Initial $MTAC_{creat}$ ↑, ultrafiltration↓<br>Follow-up $MTAC_{creat}$ =, ultrafiltration =, but ↑ at 4 years<br>Sodium sieving and free water transport = to ↓<br>small pore fluid transport: gradual small ↓ |

L-GDP/N-pH: low GDP neutral pH; IQR: interquartile range; MTAC: mass transfer area coefficient.

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Prolonged exposure to PD solutions, possibly exacerbated by episodes of peritonitis, causes sustained inflammation and progressive damage to the peritoneal membrane, which undergoes angiogenesis, hyalinizing vasculopathy and fibrosis. These morphologic alterations have been associated with increased PSTR and UF failure, thereby constituting a major barrier to longterm PD, through an increased risk of technique failure, morbidity (including increased risk of EPS) and mortality.

The role of peritonitis in developing EPS is less clear, partly because it often precludes long-term PD. It should be pointed out that the morphological features of EPS are different to those of progressive fibrosis, characterized by inflammation, fibrin deposition and expression of thrombospondin and that there is no role for routine peritoneal biopsy in the prediction of this condition.

GRUPPO di PROGETTO di DIALISI PERITONEA
SOCIETA' ITALIANA di NEFROLOGIA

# CENSIMENTO GPDP 2022

## PERITONITI – 225 CENTRI

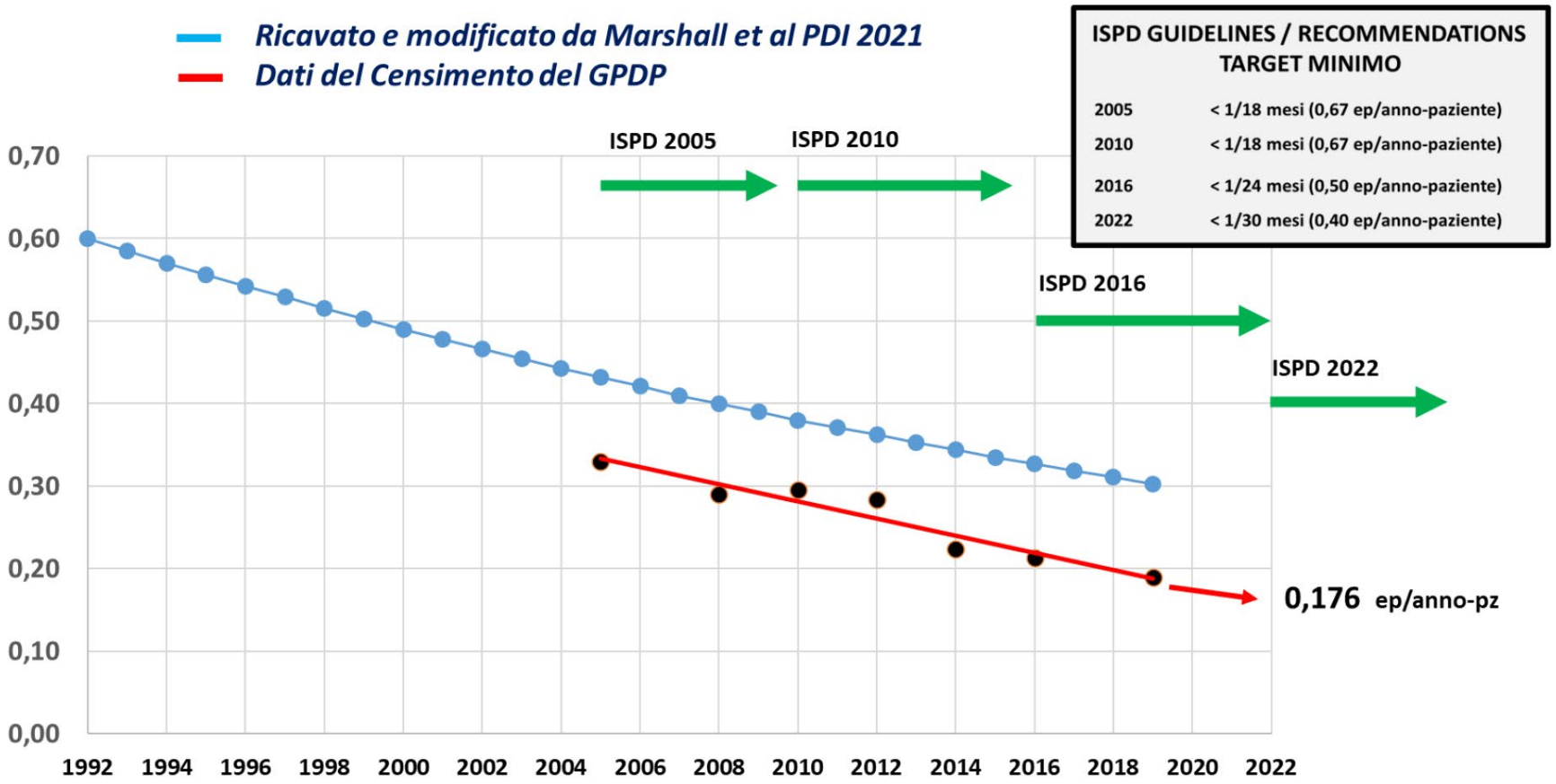
| | INCIDENZA | | | |
|---|---|---|---|---|
| | PERITONITI | ep/anno-pz | mesi-pz/ep | NEG. (%) |
| 2008 | 1171 | 0,290 | **41,1** | 17,1 |
| 2010 | 1208 | 0,296 | **40,5** | 18,5 |
| 2012 | 1179 | 0,284 | **42,3** | 15,9 |
| 2014 | 953 | 0,224 | **53,5** | 19,9 |
| 2016 | 940 | 0,213 | **56,3** | 17,3 |
| 2019 | 610 | 0,188 | **63,8** | 19,2 |
| 2022 | **694** | **0,176** | **68,2** | **19,3** |

**3.942,5 ANNI-PZ**
CALCOLO DEL FOLLOW UP CON IL METODO TRADIZIONALE
-
IL METODO TRADIZIONALE SEMBRA SOTTOSTIMARE IL FOLLOW UP DEL 5,4% RISPETTO IL «GOLD STANDARD» 2.2 (differenza ingresso e uscita per ogni paziente)
NB – sottostima del tempo = sovrastima dell'incidenza

NOTE
* NEL 2019 I DATI ERANO RIFERITI A 189 CENTRI

# INCIDENZA DELLE PERITONITI NEL TEMPO

## L'INCIDENZA NEL TEMPO DAI DATI DEI REGISTRI



# CENSIMENTO GSDP 2022

## PERITONITE SCLEROSANTE

## 227 CENTRI

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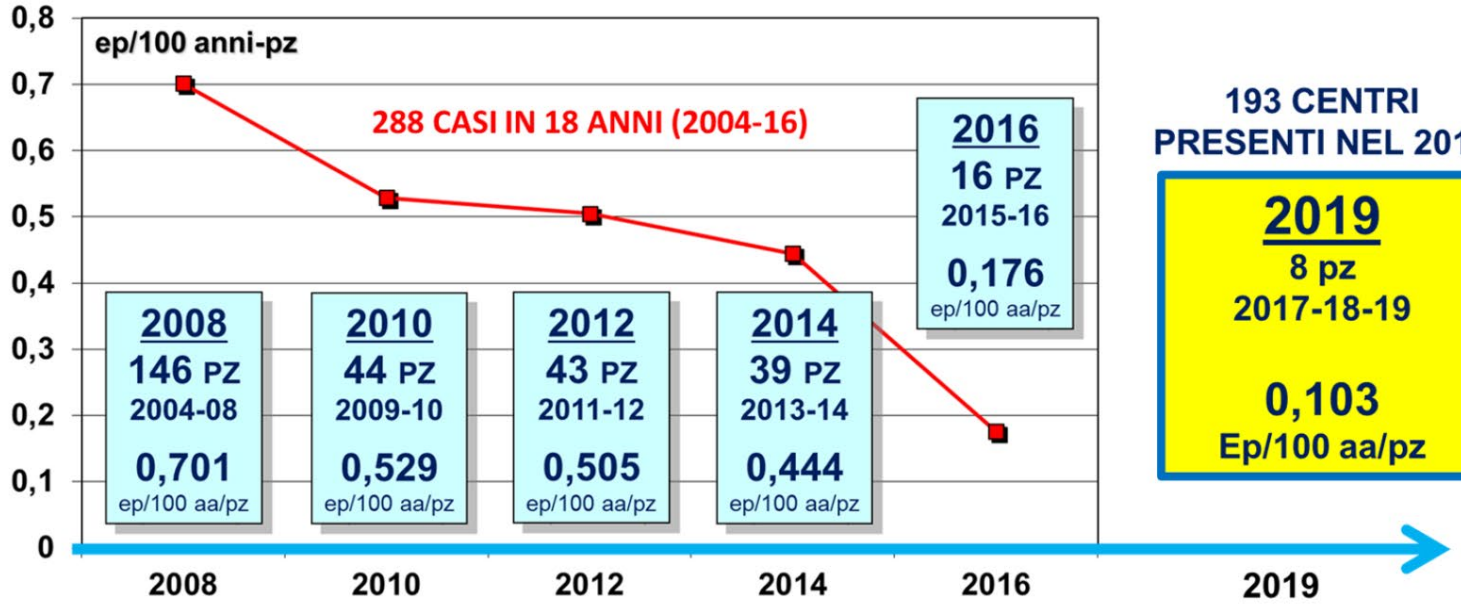


**193 CENTRI PRESENTI NEL 2016**

**2019**
**8 pz**
**2017-18-19**

**0,103**
**Ep/100 aa/pz**

**2022**

**7 pz ?**

**2020-21-22**

5 in DP - 2 in HD
0 in TX

Chirurgia = 3

Guarigione = 1
Stabilizzazione = 5
Peggioramento = 1

ep/100 aa/pz = [ (CASI PER PERIODO) / (N° ANNI PERIODO) / (PREVALENZA MEDIA DEL PERIODO) ] x 100

PREVALENZA MEDIA DEL PERIODO = (PREVAL 01/01 INIZIO + PREVAL 31/12 FINE) / (NUMERO ANNI DEL PERIODO)
PER IL 2019 SI E' TENUTO CONTO DEL DIVERSO FOLLOW UP DI RIFERIMENTO (2 O 3 ANNI) NELLE DUE MODALITA' DI INVIO DEI DATI

# Strategie e terapie contro danno di membrana e EPS

"data di scadenza" per la PD: un concetto errato (e pericoloso)

valutazione membrane disfunction, sodium sieving, sodium dip

utilizzo soluzioni biocompatibili

prevenzione e terapia accurate delle peritoniti

➡ ipertensione: si ACE-I o ARB; attenzione ai β-bloccanti

possibile profilassi con tamoxifene nei casi a rischio

trapianto dopo PD: alto rischio con CNI in assenza di mTOR-I

## Il blocco del sistema Renina-Angiotensina-Aldosterone previene la fibrosi peritoneale. Studi su colture cellulari.

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## Il blocco del sistema Renina-Angiotensina-Aldosterone previene la fibrosi peritoneale e il deficit di ultrafiltrazione. Studi in modelli animali.

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# Angiotensin II Facilitates Fibrogenic Effect of TGF-β1 through Enhancing the Down-Regulation of BAMBI Caused by LPS: A New Pro-Fibrotic Mechanism of Angiotensin II

PLOS ONE October 2013 | Volume 8 | Issue 10 | e76289

Yu-Sheng Li[1*☯], Shu-Yuan Ni[2☯], Ying Meng[3☯], Xiao-Lan Shi[1], Xu-Wen Zhao[1], Hai-Hua Luo[1], Xu Li[4*]

Angiotensin II has progressively been considered to play an important role in the development of liver fibrosis, although the mechanism isn't fully understood. The aim of this study was to investigate a possible pro-fibrotic mechanism, by which angiotensin II would enhance the pro-fibrotic effect of transforming growth factor beta 1 (TGF-β1) through up-regulation of toll-like receptor 4 (TLR4) and enhancing down-regulation of TGF-β1 inhibitory pseudo-receptor—BAMBI caused by LPS in hepatic stellate cells (HSCs). Firstly, the synergistic effects of angiotensin II, TGF-β1 and LPS on collagen 1α production were confirmed in vitro by ELISA, in which angiotensin II, LPS and TGF-β1 were treated sequentially, and in vivo by mmunofluorescence, in the experiments single or multiple intra-peritoneally implanted osmotic mini-pumps administrating angiotensin II or LPS combined with intra-peritoneal injections of TGF-β1 were used. We also found that only LPS and TGFβ1 weren't enough to induce obvious fibrogenesis without angiotensin II. Secondly, to identify the reason of why angiotensin II is so important, the minute level of TLR4 in activated HSCs - T6 and primary quiescent HSCs of rat, upregulation of TLR4 by angiotensin II and blockage by different angiotensin II receptor type 1 (AT1) blockers in HSCs were assayed by western blotting in vitro and immunofluorescence in vivo. Finally, BAMBI expression level, which is regulated by LPS-TLR4 pathway, was detected by qRT-PCR and results showed angiotensin II enhanced the down-regulation of BAMBI mRNA caused by LPS in vitro and in vivo, and TLR4 neutralization antibody blocked this interactive effect. These data demonstrated that angiotensin II enhances LPS-TLR4 pathway signaling and further down-regulates expression of BAMBI through up-regulation of TLR4, which results in facilitation of pro-fibrotic activity of TGF-β1. Angiotensin II, LPS and TGF-β1 act synergistically during hepatic fibrogenesis, showing crosstalks between angiotensin II-AT1, LPS-TLR4 and TGF-β1-BAMBI signal pathways in rat HSCs.

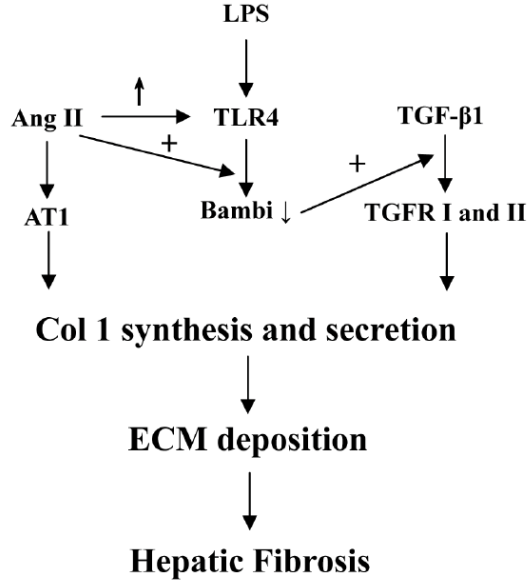


**Figure 6. Crosstalk between Ang II and TGF-β1 is supported by the LPS-TLR4-BAMBI signal pathway in HSCs.** Ang II induces Col 1 synthesis in, and secretion from, HSCs through AT1, so does TGF-β1 through TGFR I and II. LPS doesn't induce Col 1 synthesis and secretion in HSCs directly through TLR4, but LPS-TLR4 interaction down-regulates BAMBI expression, which is a TGF-β1 pseudo-receptor. Then the pro-fibrogenic function of TGF-β1 is enhanced. Ang II up-regulates TLR4 expression and enhances the activity of LPS-TLR4 signal pathway in HSCs, resulting in further down-regulation of BAMBI expression and up-regulated pro-fibrogenic function of TGF-β1. ↑ represents upregulation; ↓ represents downregulation; + represents enhancement.

## Valsartan ameliorates high glucose-induced peritoneal fibrosis by blocking mTORC1 signaling

*Experimental Biology and Medicine* 2020; 245: 983–993

Jing Liu, Yuan Feng, Cheng Sun, Wei Zhu, Qing-Yan Zhang, Bo Jin, Qiu-Yuan Shao, Yang-Yang Xia, Peng-Fei Xu, Miao Zhang and Chun-Ming Jiang

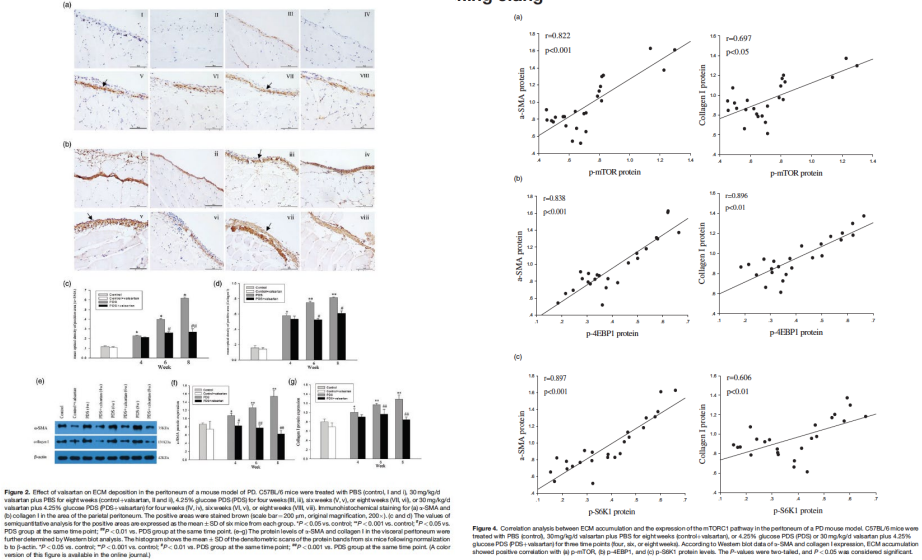

Figure 2. Effect of valsartan on ECM deposition in the peritoneum of a mouse model of PD. C57BL/6 mice were treated with PBS (control, I and i), 30 mg/kg/d valsartan plus PBS for eight weeks (control + valsartan, II and ii), 4.25% glucose PDS (PDS) for four weeks (III, iii), six weeks (V, v), or eight weeks (VII, vii), or 30 mg/kg/d valsartan plus 4.25% glucose PDS (PDS + valsartan) for four weeks (IV, iv), six weeks (VI, vi), or eight weeks (VIII, viii). Immunohistochemical staining for (a) α-SMA and (b) collagen I in the area of the parietal peritoneum. The positive areas were stained brown (scale bar = 200 μm, original magnification, 200×). (c and d) The values of semiquantitative analysis for the positive areas are expressed as the mean ± SD of six mice from each group. *P < 0.05 vs. control; **P < 0.001 vs. control; #P < 0.05 vs. PDS group at the same time point; ##P < 0.01 vs. PDS group at the same time point. (e–g) The protein levels of α-SMA and collagen I in the visceral peritoneum were further determined by Western blot analysis. The histogram shows the mean ± SD of the densitometric scans of the protein bands from six mice following normalization to b-actin. *P < 0.05 vs. control; **P < 0.001 vs. control; #P < 0.01 vs. PDS group at the same time point; ##P < 0.001 vs. PDS group at the same time point. (A color version of this figure is available in the online journal.)



Figure 4. Correlation analysis between ECM accumulation and the expression of the mTORC1 pathway in the peritoneum of a PD mouse model. C57BL/6 mice were treated with PBS (control), 30 mg/kg/d valsartan plus PBS for eight weeks (control + valsartan), or 4.25% glucose PDS (PDS) or 30 mg/kg/d valsartan plus 4.25% glucose PDS (PDS + valsartan) for three time points (four, six, or eight weeks). According to Western blot data of α-SMA and collagen I expression, ECM accumulation showed positive correlation with (a) p-mTOR, (b) p-4EBP1, and (c) p-S6K1 protein levels. The *P*-values were two-tailed, and $P < 0.05$ was considered significant.

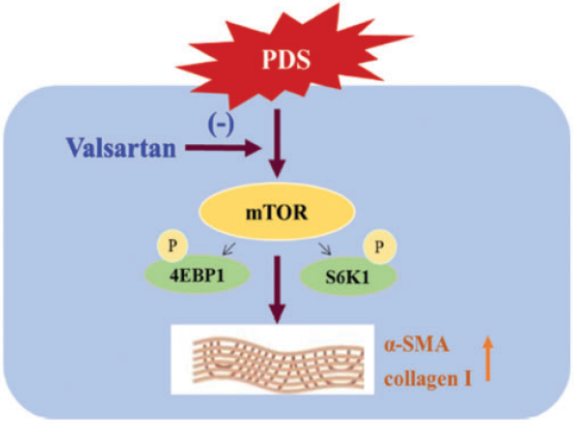


**Figure 7.** Schematic model of the protective mechanism of valsartan against HG-induced PF in PMCs. Valsartan significantly inhibits HG-induced ECM accumulation in the peritoneum, which manifests as decreased expression levels of α-SMA and collagen I. These effects are correlated with a decrease in the expression of the mTORC1 pathway, which is mediated by the downregulation of p-mTOR, p-4EBP1, and p-S6K1 levels. Overall, valsartan exerts an obvious protective effect against HG-induced PF, which is partly due to the inhibition of the mTORC1 pathway in PMCs. (A color version of this figure is available in the online journal.)

the present study demonstrated that high glucose-related peritoneal fibrosis is closely associated with the activation of mTORC1. Valsartan can control PF and is associated with the inhibition of mTORC1 activity. Altogether, our data provide new insight into the mechanism underlying the preservation of the peritoneum by valsartan and supply a foundation for therapeutic strategies for longterm PD patients.

# I β-bloccanti favoriscono la fibrosi peritoneale e il deficit di ultrafiltrazione

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# Nebivolol, a $\beta_1$-adrenergic blocker, protects from peritoneal membrane damage induced during peritoneal dialysis

Georgios Liappas[1,*], Guadalupe González-Mateo[1,*], Anna Rita Aguirre[2,*], Hugo Abensur[2], Patricia Albar-Vizcaino[3], Emilio González Parra[4], Pilar Sandoval[1], Laura García Ramírez[3], Gloria del Peso[5], Juan Manuel Acedo[6], María A. Bajo[5], Rafael Selgas[5], José A. Sánchez Tomero[3], Manuel López-Cabrera[1] and Abelardo Aguilera[3]

**Oncotarget, Vol. 7, No. 21**

***Published:*** *April 18, 2016*

β-blockers have been considered deleterious for PM due to their association with loss of UFC and induction of fibrosis. Herein we analyzed the effects of Nebivolol, a new generation of β1-blocker, on PM alterations induced by PD fluids (PDF).

*In vitro:* We found that mesothelial cells (MCs) express β1-adrenergic receptor. MCs were treated with TGF-β to induce mesothelial-to-mesenchymal transition (MMT) and co-treated with Nebivolol. Nebivolol reversed the TGF-β effects, decreasing extracellular matrix synthesis, and improved the fibrinolytic capacity, decreasing plasminogen activator inhibitor-1 (PAI-1) and increasing tissue-type plasminogen activator (tPA) supernatant levels. Moreover, Nebivolol partially inhibited MMT and decreased vascular endothelial growth factor (VEGF) and IL-6 levels in supernatants.

*In vivo*: Twenty-one C57BL/6 mice were divided into 3 groups. Control group carried a catheter without PDF infusion. Study group received intraperitoneally PDF and oral Nebivolol during 30 days. PDF group received PDF alone. Nebivolol maintained the UFC and reduced PM thickness, MMT and angiogenesis promoted by PDF. It also improved the fibrinolytic capacity in PD effluents decreasing PAI-1 and IL-8 and increased tPA levels.

*Conclusion:* Nebivolol protects PM from PDF-induced damage, promoting anti-fibrotic, anti-angiogenic, anti-inflammatory and pro-fibrinolytic effects.

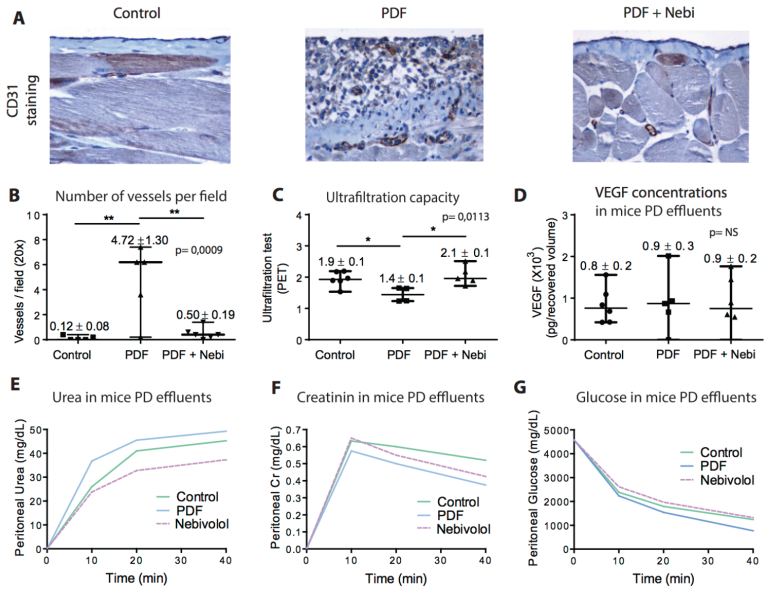


**Figure 4: *In vivo* analysis of the alterations related to angiogenesis and the ultrafiltration capacity of the peritoneal membrane. A.** Immunohistochemistry staining of CD31 (vessels) and **B.** quantification of the total CD31 positive stained cells in the peritoneal membrane. **C.** Ultrafiltration capacity analysis (PET test) (30 minutes) after injecting mice with PDF in the last day of the experiment. **D.** Concentrations of VEGF (pg/recovered volume) measured by ELISA in the peritoneal effluents of mice. No significant (NS) differences were observed. **E.-G.** Kinetic curves of urea, creatinine and glucose, respectively, in the different groups of mice measured at 10, 20 and 40 minutes. Data point graphics represent the absolute value of each determination and lines the median, lower and upper range. Numbers on the top of graphics represent the mean ± SE. *P* values < 0.05 are considered statistically significant using one-way Anova test, and are depicted in the graphs. To account for multiple comparisons, the Bonferroni post-test was used to compare all pairs of means. NE: MCs with non-epithelioid phenotype. The symbols represent the statistical differences between the groups (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

# Strategie e terapie contro danno di membrana e EPS

"data di scadenza" per la PD: un concetto errato (e pericoloso)

valutazione membrane disfunction, sodium sieving, sodium dip

utilizzo soluzioni biocompatibili

prevenzione e terapia accurate delle peritoniti

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trapianto dopo PD: alto rischio con CNI in assenza di mTOR-I

*Perit Dial Int* 2014; 34(6):582–593

# CAN EPS DEVELOPMENT BE AVOIDED WITH EARLY INTERVENTIONS? THE POTENTIAL ROLE OF TAMOXIFEN—A SINGLE-CENTER STUDY

Erika De Sousa–Amorim,[1] Gloria Del Peso,[1] M. Auxiliadora Bajo,[1] Laura Alvarez,[1] Marta Ossorio,[1] Fernando Gil,[2] Teresa Bellon,[3] and Rafael Selgas[1]

♦ *Methods:* For a 30-year period representing our entire PD experience, we retrospectively identified all patients with EPS (diagnosed according to International Society for Peritoneal Dialysis criteria) and all patients defined as EPS-prone because they met at least 2 established criteria (severe peritonitis, PD vintage greater than 3 years, severe hemoperitoneum, overexposure to glucose, and acquired ultrafiltration failure).

♦ *Results:* Of 679 PD patients, we identified 20 with EPS, for an overall prevalence of 2.9%. Mean age at diagnosis was 50.2 ± 16.4 years, with a median PD time of 77.96 months (range: 44.36 – 102.7 months) and a median follow-up of 30.91 months (range: 4.6 – 68.75 months). Of patients with EPS, 10 (50%) received tamoxifen, 10 (50%) received parenteral nutrition, and 2 (10%) underwent adhesiolysis, with 25% mortality related to EPS. Another 14 patients were identified as EPS-prone. Median follow-up was 54.05 months (range: 11.9 – 87.04 months). All received tamoxifen, and 5 (36%) received corticosteroids; none progressed to full EPS. We observed no differences in baseline data between the groups, but the group with EPS had been on PD longer (84 ± 53 months vs 39 ± 20 months, $p = 0.002$) and had a higher cumulative number of days of peritoneal inflammation from peritonitis (17.2 ± 11.1 days vs 9.8 ± 7.9 days, $p = 0.015$). Overall mortality was similar in the groups. The incidence of EPS declined during our three decades of experience (5.6%, 3.9%, and 0.3%).

♦ *Conclusions:* Being a serious, life-threatening complication of PD, EPS requires high suspicion to allow for prompt diagnosis and treatment. Early detection of EPS-prone states and delivery of appropriate intervention might prevent EPS development. Tamoxifen seems to be a key strategy in prevention, but caution should be used in interpreting our results. Additional randomized controlled studies are needed.

Demographics and Peritoneal Functional Data

| Variable | Prone to EPS | With EPS | *p* Value |
|---|---|---|---|
| Patients (*n*) | 14 | 20 | |
| Mean age (years) | 42.02±21.46 | 50.22±16.44 | NS |
| Sex [*n* (%) women] | 5 (35.7) | 14 (70) | NS |
| Diabetes [*n* (%)] | 1 (7.1) | 2 (10) | NS |
| Peritoneal dialysis | | | |
| Modality [*n* (%) CAPD] | 5 (37.5) | 13 (65) | NS |
| Vintage (months) | | | |
| Median | 37.88 | 77.96 | 0.002 |
| Range | 24.76–51.45 | 44.36–102.7 | |
| MTAC | | | |
| Urea | | | |
| Basal (*n*=39) | 22.18±7.07 | 23.31±7.85 | NS |
| Final (*n*=36) | 19.49±4.84 | 20.36±6.27 | NS |
| Creatinine | | | |
| Basal (*n*=39) | 10.73±5.67 | 11.45±5.75 | NS |
| Final (*n*=36) | 11.46±3.09 | 12.02±3.58 | NS |
| Ultrafiltration (mL) | | | |
| Basal (*n*=39) | 666.43±350.9 | 808.33±362.28 | NS |
| Final (*n*=34) | 185±379.36 | 400.88±290.95 | NS |
| D/P creatinine | | | |
| Basal (*n*=39) | 0.70±0.11 | 0.72±0.11 | NS |
| Final (*n*=36) | 0.72±0.16 | 0.76±0.08 | NS |
| Peritonitis | | | |
| Patients [*n* (%)] | 14 (100) | 17 (85) | NS |
| Cumulative days | | | 0.015 |
| Median | 7 | 17 | |
| Range | 5–14 | 10–21 | |
| Episodes | 2.21±2.15 | 3.35±3.1 | NS |
| Follow-up after Dx (months) | | | |
| Median | 54.05 | 30.91 | NS |
| Range | 11.9–87.04 | 4.6–68.75 | |

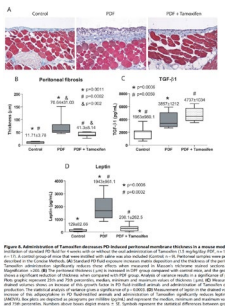
EPS = encapsulating peritoneal sclerosis; NS = nonsignificant; CAPD = chronic ambulatory peritoneal dialysis; MTAC = mass transfer area coefficient; D/P = dialysate-to-plasma ratio; Dx = diagnosis.

PLOS ONE

April 2013 | Volume 8 | Issue 4 | e61165

# Tamoxifen Ameliorates Peritoneal Membrane Damage by Blocking Mesothelial to Mesenchymal Transition in Peritoneal Dialysis

**Jesús Loureiro[1☯], Pilar Sandoval[1☯], Gloria del Peso[2], Guadalupe Gónzalez-Mateo[2], Vanessa Fernández-Millara[2], Beatríz Santamaria[3], Maria Auxiliadora Bajo[2], José Antonio Sánchez-Tomero[4], Gonzalo Guerra-Azcona[5], Rafael Selgas[2], Manuel López-Cabrera[1], Abelardo I. Aguilera[4]***

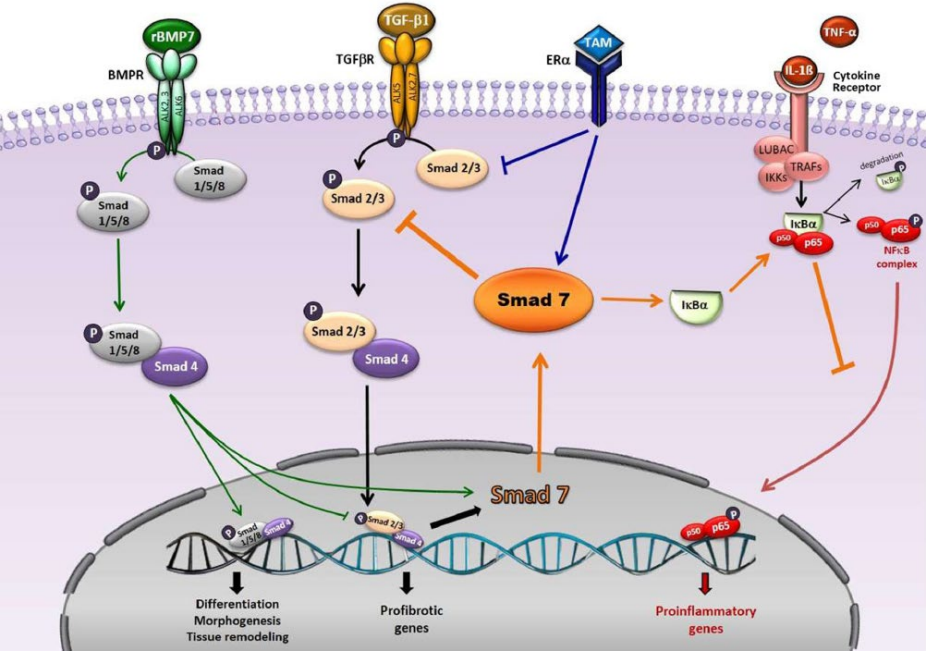


Mesothelial-to-mesenchymal transition (MMT) is an auto-regulated physiological process of tissue repair that in uncontrolled conditions such as peritoneal dialysis (PD) can lead to peritoneal fibrosis. The maximum expression of peritoneal fibrosis induced by PD fluids and other peritoneal processes is the encapsulating peritoneal sclerosis (EPS) for which no specific treatment exists. Tamoxifen, a synthetic estrogen, has successfully been used to treat retroperitoneal fibrosis and EPS associated with PD. Hence, we used *in vitro* and animal model approaches to evaluate the efficacy of Tamoxifen to inhibit the MMT as a trigger of peritoneal fibrosis. *In vitro* studies were carried out using omentum-derived mesothelial cells (MCs) and effluent-derived MCs. Tamoxifen blocked the MMT induced by transforming growth factor (TGF)-β1, as it preserved the expression of E-cadherin and reduced the expression of mesenchymal-associated molecules such as snail, fibronectin, collagen-I, α-smooth muscle actin, and matrix metalloproteinse-2. Tamoxifen-treatment preserved the fibrinolytic capacity of MCs treated with TGF-β1 and decreased their migration capacity. Tamoxifen did not reverse the MMT of non-epitheliod MCs from effluents, but it reduced the expression of some mesenchymal molecules. In mice PD model, we demonstrated that MMT progressed in parallel with peritoneal membrane thickness. In addition, we observed that Tamoxifen significantly reduced peritoneal thickness, angiogenesis, invasion of the compact zone by mesenchymal MCs and improved peritoneal function. Tamoxifen also reduced the effluent levels of vascular endothelial growth factor and leptin. These results demonstrate that Tamoxifen is a therapeutic option to treat peritoneal fibrosis, and that its protective effect is mediated via modulation of the MMT process.

*Molecular Medicine* (2019) 25:41

# Tamoxifen and bone morphogenic protein-7 modulate fibrosis and inflammation in the peritoneal fibrosis model developed in uremic rats

Filipe M. O. Silva[1], Elerson C. Costalonga[1], Cleonice Silva[1], Ana C. O. Carreira[2,3], Samirah A. Gomes[1], Mari C. Sogayar[2,4], Camilla Fanelli[1] and Irene L. Noronha[1*]



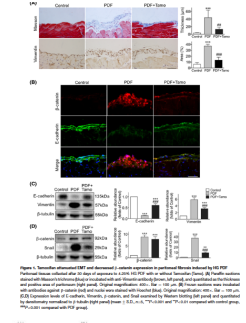

Methods: To mimic the clinical situation of patients on long-term PD, a combo model, characterized by the combination of PF and CKD with severe uremia, was developed in Wistar rats. PF was induced by intraperitoneal (IP) injections of chlorhexidine gluconate (CG), and CKD was induced by an adenine-rich diet. Uremia was confirmed by severe hypertension, increased blood urea nitrogen (BUN> 120 mg/dL) and serum creatinine levels (> 2 mg/dL). Uremic rats with PF were treated with TAM (10 mg/Kg by gavage) or BMP7 (30 µg/Kg, IP). Animals were followed up for 30 days.

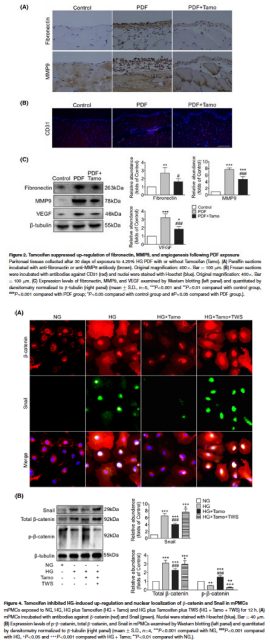
Results: CG administration in uremic rats induced a striking increase in PM thickness, neoangiogenesis, demonstrated by increased capillary density, and failure of ultrafiltration capacity. These morphological and functional changes were blocked by TAM or rBMP7 treatment. In parallel, TAM and rBMP7 significantly ameliorated the PM fibrotic response by reducing α-SMA, extracellular matrix proteins and TGF-ß expression. TAM or rBMP7 administration significantly inhibited peritoneal Smad3 expression in uremic rats with PF, prevented Smad3 phosphorylation, and induced a remarkable upregulation of Smad7, an intracellular inhibitor of TGFβ/Smad signaling, contributing to a negative modulation of profibrotic genes. Both treatments were also effective in reducing local inflammation, possibly by upregulating IκB-α expression in the PM of uremic rats with PF. In vitro experiments using primary peritoneal fibroblasts activated by TGF-ß confirmed the capacity of TAM or rBMP7 in blocking inflammatory mediators, such as IL-1ß expression.

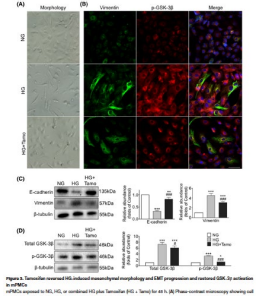
*Bioscience Reports* (2018) **38** BSR20180240
https://doi.org/10.1042/BSR20180240

# Tamoxifen attenuates dialysate-induced peritoneal fibrosis by inhibiting GSK-3β/β-catenin axis activation

Pengpeng Yan[1,*], Huanna Tang[1,*], Xiaoying Chen[1], Shuiyu Ji[2], Wei Jin[3], Jiaming Zhang[2], Jia Shen[1], Hao Deng[1], Xiang Zhao[2], Quanquan Shen[2] and Hongfeng Huang[1]







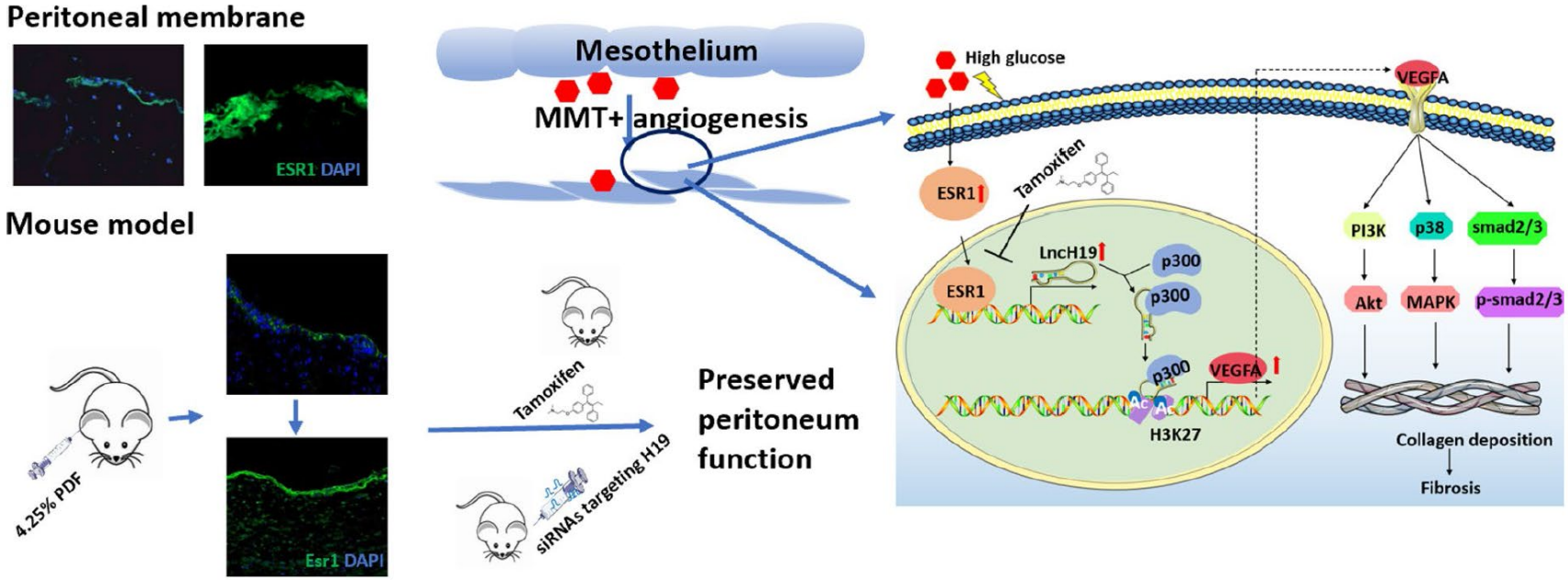


Peritoneal fibrosis is a severe complication arising from long-term peritoneal dialysis (PD). Tamoxifen (Tamo) has been clinically proven effective in a series of fibrotic diseases, such as PD-associated encapsulating peritoneal sclerosis (EPS), but the mechanisms underlying Tamoxifen's protective effects are yet to be defined. In the present study, C57BL/6 mice received intraperitoneal injections of either saline, 4.25% high glucose (HG) PD fluid (PDF) or PDF plus Tamoxifen each day for 30 days. Tamoxifen attenuated thickening of the peritoneum, and reversed PDF-induced peritoneal expression of E-cadherin, Vimentin, matrix metalloproteinase 9 (MMP9), Snail, and β-catenin. Mouse peritoneal mesothelial cells (mPMCs) were cultured in 4.25% glucose or 4.25% glucose plus Tamoxifen for 48 h. Tamoxifen inhibited epithelial-to-mesenchymal transition (EMT) as well as phosphorylation of glycogen synthase kinase-3β (GSK-3β), nuclear β-catenin, and Snail induced by exposure to HG. TWS119 reversed the effects of Tamoxifen on β-catenin and Snail expression. In conclusion, Tamoxifen significantly attenuated EMT during peritoneal epithelial fibrosis, in part by inhibiting GSK-3β/β-catenin activation.

# Tamoxifen exerts anti-peritoneal fibrosis effects by inhibiting H19-activated *VEGFA* transcription

*Journal of Translational Medicine* (2023) 21:614

Tingting Zhao[1,2†], Zhengyu Sun[1†], Xueli Lai[1†], Hongtao Lu[3†], Lulu Liu[1], Shuangxi Li[1], Ji-hang Yuan[4*] and Zhiyong Guo[1*]




ESR1 was increased significantly in the peritoneum after long-term exposure to PD dialysate. Tamoxifen treatment ameliorated high glucose-induced MMT of HPMCs, improved ultrafiltration rate, and decreased PSTR of mouse peritoneum. Tamoxifen reduced the H19 level by decreasing the ESR1 transcription of H19. Depletion of H19 reversed the pro-fibrotic effect of high glucose while ectopic expression of H19 exacerbated fibrotic pathological changes. Intraperitoneal injection of nanomaterial-wrapped 2′-O-Me-modified siRNAs targeting H19 mitigated PD-related fibrosis in mice. RNA immunoprecipitation (RIP) and RNA pull-down results delineated that H19 activated VEGFA expression by binding p300 to the VEGFA promoter and inducing histone acetylation of the VEGFA promoter. ESR1 and H19 were promising targets to predict peritoneal function.

# Esperienza clinica con Tamoxifene nell'EPS


Eltoum MA et al: Four consecutive cases of peritoneal dialysis-related encapsulating peritoneal sclerosis treated successfully with tamoxifen. Perit Dial Int 2006;26:203-206

Moustafellos P et al: Tamoxifen therapy in Encapsulating Sclerosing Peritonitis in patients after kidney transplantation. Transplant Proc 2006;38:2913-2914

Wong CF: Clinical experience with tamoxifen in Encapsulating Peritoneal Sclerosis. Perit Dial Int 2006;26:183-184

Mohamed AO: Tamoxifen therapy in kidney-transplant patients presenting with severe Encapsulating Peritoneal Sclerosis after treatment of acute humoral rejection. Exper Clin Transplant 2009;3:164-167

Korte MR et al: Tamoxifen is associated with lower mortality of encapsulating peritoneal sclerosis: results of the Dutch Multicentre EPS Study. Nephrol Dial Transplant 2011;26:691-697

Nephrol Dial Transplant (2011) 26: 691–697

# Tamoxifen is associated with lower mortality of encapsulating peritoneal sclerosis: results of the Dutch Multicentre EPS Study

Mario R. Korte[1,2], Marien W. Fieren[2], Denise E. Sampimon[3], Hester F. Lingsma[4], Willem Weimar[2], Michiel G.H. Betjes[2] and on behalf of the investigators of the Dutch Multicentre EPS Study*

**Table 1.** Patient characteristics

| | | Tamoxifen | | |
|---|---|---|---|---|
| | Total ($n$=63) | Yes ($n$=24) | No ($n$=39) | P-value |
| Gender (f/m) | 21/42 | 6/18 | 15/24 | NS |
| Age | | | | |
| Age at diagnosis EPS | 43.4 ± 14.4 | 44.7 ± 13.6 | 42.7 ± 15.1 | NS |
| Age at start PD | 34.7 ± 15.4 | 36.0 ± 14.6 | 34.3 ± 16.4 | NS |
| Age at death or end of study | 45.1 ± 14.1 | 46.4 ± 13.2 | 44.3 ± 14.8 | NS |
| Age at last transplantation | 36.4 ± 13.4 | 39.9 ± 15.1 | 34.0 ± 12.0 | NS |
| Periods | | | | |
| Time until death after EPS | 27.3 ± 20.6 | 30.8 ± 18.6 | 25.2 ± 21.7 | NS |
| Follow-up | 129.4 ± 60.5 | 134.8 ± 65.6 | 126.0 ± 57.7 | NS |
| Renal replacement when EPS | | | | |
| PD | 16 | 7 | 9 | NS |
| HD | 29 | 8 | 21 | NS |
| Functioning graft | 18 | 9 | 9 | NS |
| End of study | | | | |
| Deceased | 40 | 11 | 29 | 0.03 |
| EPS related death | 35 | 11 | 24 | NS |
| Alive, functioning graft | 9 | 6 | 3 | 0.07 |
| Alive HD | 14 | 7 | 7 | NS |
| Alive, PD | 0 | 0 | 0 | NS |

Data shown as means ± SD. f, female; m, male. Age expressed in years. Time periods expressed in months. Renal replacement therapy expressed in number of patients. Means were compared using unpaired $t$-tests. Proportions were compared with chi-square tests. A two-sided P-value of <0.05 was considered to be statistically significant. NS, not significant.

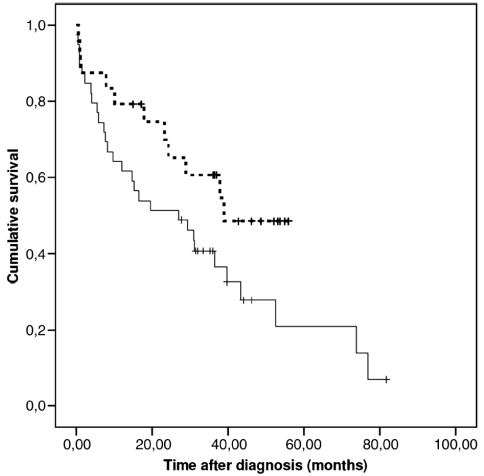



**Fig. 1.** Survival of EPS patients with and without treatment with tamoxifen. Kaplan–Meier analysis showing survival of 24 patients treated with tamoxifen (dashed line) and 39 patients without tamoxifen (solid line). Time after diagnosis means time in months after EPS diagnosis. + Means censored in analysis. P-value was 0.077.

**Table 3.** Treatment of EPS

| | Tamoxifen | | |
|---|---|---|---|
| Treatment for EPS | Yes ($n$=24) | No ($n$=39) | P-value |
| Parenteral nutrition | 14 | 21 | NS |
| Prednisone | 11 | 9 | NS |
| Azathioprine | 1 | 1 | NS |
| Prednisone total use | 12 | 14 | NS |

Data shown as number of patients. Prednisone total use means patients treated with prednisone because of EPS and because of renal transplant after the moment of EPS diagnosis. Proportions were compared with chi-square tests. A two-sided P-value of <0.05 was considered to be statistically significant. NS, not significant.

# Tamoxifene nell'EPS: possibili effetti collaterali

Juric C et al: First documented case of endometrial carcinoma in a patient treated with tamoxifen for Encapsulating Peritoneal Sclerosis. Perit Dial Int 2013;33:338-339

Kwak KM et al: Liver infarction and venous thromboembolism after tamoxifen use in an ADPKD patient with Encapsulating Peritoneal Sclerosis: a case report. Electrolyte Blood Press 2020;18:44-48

Utili:
- Sorveglianza con PAP-test annuale nella donna
- Screening fattori di rischio per tromboembolismo

*BMC Nephrology* (2020) 21:110

# 10-year-long survival in a PD patient with severe calcifying encapsulating peritoneal sclerosis treated with tamoxifen: a case-report

Vassilios Liakopoulos*, Panagiotis I. Georgianos, Vasilios Vaios, Stefanos Roumeliotis, Apostolos Karligkiotis and Pantelis E. Zebekakis

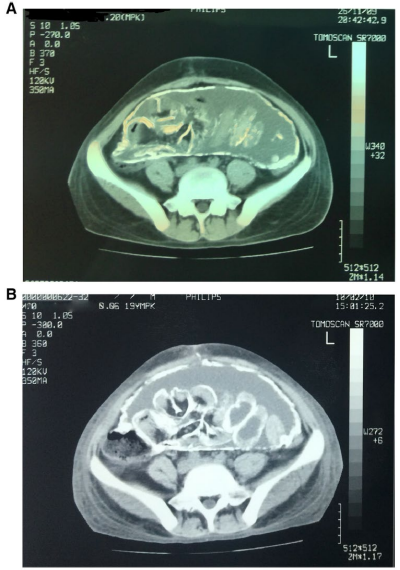



**Fig. 1 a** Abdominal CT scan (Nov 2009) showing excessive peritoneal thickening, multiple intra-abdominal adhesions of bowel loops and a calcified fibrous cocoon wrapped around the bowel; **b** abdominal CT scan (Feb 2010) showing persistence of calcified intra-abdominal lesions and peritoneal thickening

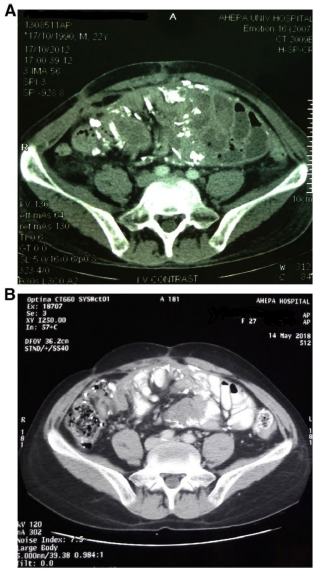



**Fig. 2 a** Abdominal CT scan after the discontinuation of steroids (Oct 2012) showing a similar radiological picture in comparison with earlier CT scans; b abdominal CT scan (May 2018) showing minimal improvement of the radiological picture over a 10-year-long follow-up. The high density in (**b**) is due to oral intake of a water-soluble contrast agent for the abdominal CT scan evaluation

We report the case of a 28-year-old patient, who developed a severe form of calcifying EPS after a 6-year-long therapy with automated PD. The clinical presentation was severe with repeated episodes of total bowel obstruction, weight loss and malnutrition that mandated his prolonged hospitalization. Initial treatment included corticosteroids and tamoxifen (20 mg/day) with a clinically meaningful improvement in gastrointestinal function and nutritional status over the first 6–12 months. Corticosteroids were discontinued at 18 months, but owing to persistence of calcifying lesions and peritoneal thickening in repeated computed-tomography (CT) scans, tamoxifen remained unmodified at a low-dose of 20 mg/day for a 10-year-long period. During follow-up, the patient remained symptoms-free in an excellent clinical condition and the CT findings were unchanged.

# Strategie e terapie contro danno di membrana e EPS

"data di scadenza" per la PD: un concetto errato (e pericoloso)

valutazione membrane disfunction, sodium sieving, sodium dip

utilizzo soluzioni biocompatibili

prevenzione e terapia accurate delle peritoniti

ipertensione: si ACE-I o ARB; attenzione ai β-bloccanti

possibile profilassi con tamoxifene nei casi a rischio

➡ trapianto dopo PD: alto rischio con CNI in assenza di mTOR-I

# Induzione della fibrosi con CNI: meccanismi

- Aumento di trascrizione di TGF-β
- Aumento dell'espressione dei recettori per TGF-β
- Aumento di trascrizione di VEGF
- Aumento dell'espressione dei recettori per VEGF

Van Nieuwenhoven FA et al: Imbalance of growth factors signalling in diabetic kidney disease: is connective tissue growth factor (CTGF, CCN2) the perfect intervention point? Nephrol Dial Transplant 2005;20:6-10

Myers BD et al: Cyclosporine-associated chronic nephropathy. N Eng J Med 1984;31:699-705

Shibab FS et al: Role of transforming growth factor-b1 in experimental chronic cyclosporin nephropathy. Kidney Int 1996;49:1141-51

Shin GT et al: In vivo expression of transforming growth factor-b in humans. Transplantation 1998;65:3313-18

Shibab FS et al: Expression of vascular endothelial growth factor and its receptors Flt-1 and KDR/FLK-1 in chronic cyclosporin nephrotoxicity. Transplantation 2001;72:164-168

# Induzione della fibrosi peritoneale con CNI: studi su modelli animali

## Cyclosporin A Induces Peritoneal Fibrosis and Angiogenesis during Chronic Peritoneal Exposure to a Glucose-Based, Lactate-Buffered Dialysis Solution in the Rat

Roos van Westrhenen[a] Jan Aten[b] Najat Hajji[a] Onno J. de Boer[b]
Cindy Kunne[c] Dirk R. de Waart[c] Raymond T. Krediet[a]

Blood Purif 2007;25:466–472

Background/Aims: Cyclosporin A (CsA) stimulates the development of fibrosis. We investigated whether CsA contributes to peritoneal alterations induced by long-term exposure to dialysis solutions.
Methods: Ten rats received peritoneal infusion of dialysis solution and oral CsA for 8 weeks. Eight received only the dialysis solution (controls). Peritoneal function was assessed at 8 weeks followed by sacrifice. The number of vessels was counted, fibrosis was assessed and hydroxyproline was determined. PCR was performed for vascular endothelial growth factor (VEGF), connective tissue growth factor (CTGF) and transforming growth factor-β (TGF-β).
Results: Histology revealed more fibrosis, hydroxyproline and vessels (thick walled) in CsA-exposed animals. Peritoneal transport was not different. The mRNA content of TGF-β, CTGF and VEGF was higher in CsA.
Conclusion: CsA combined with exposure to dialysis solutions was associated with increased peritoneal fibrosis and angiogenesis.

*Perit Dial Int* 2009; 29(S2):S206–S210

## DOES IMMUNOSUPPRESSIVE TREATMENT AMELIORATE MORPHOLOGY CHANGES IN ENCAPSULATING PERITONEAL SCLEROSIS?

Devrim Bozkurt,[1] Savas Sipahi,[1] Pinar Cetin,[2] Ender Hur,[1] Özden Özdemir,[2]
Muhittin Ertilav,[1] Sait Sen,[3] and Soner Duman[1]

Encapsulating peritoneal sclerosis (EPS) is a clinical syndrome associated with ileus symptoms and irreversible sclerosis of the peritoneal membrane. Inflammation, fibrosis, and neoangiogenesis are the main features of the pathophysiology. No evidence-based therapy is currently available for EPS. In recent years, anti-inflammatory and immunosuppressive (IS) treatment modalities have become more popular. The aim of the present study was to investigate the effects of various IS treatment strategies—glucocorticosteroid (GC), azathiopurine (AZT), and cyclosporin (CsA)— on regression of EPS.
We divided 52 nonuremic Wistar albino rats into six groups: Control group—2 mL isotonic saline injected intraperitoneally (IP) daily for 3 weeks; CG group—2 mL/200 g 0.1% chlorhexidine gluconate (CG) and 15% ethanol dissolved in saline injected IP daily for 3 weeks; Resting group—CG (weeks 1 – 3), plus peritoneal rest (weeks 4 – 6); Corticosteroid (GC) group—CG (weeks 1 – 3), plus 10 mg/L prednisolone in drinking water (weeks 4 – 6); AZT group— CG (weeks 1 – 3), plus 100 mg/L azathioprine in drinking water (weeks 4 – 6); and CsA group—CG (weeks 1 – 3), plus cyclosporin 7.5 mg/kg by subcutaneous injection daily (weeks 4 – 6).
At the end of the study, under ketamine HCl anesthesia, the rats were humanely killed by bleeding. Parietal peritoneal samples were then taken from same location (away from the injection site) and changes of parietal peritoneum morphology were examined by a single pathologist.
The CG severely disturbed parameters of peritoneal morphology, increasing peritoneal thickness, inflammatory activity, vascularity, and fibrosis score as compared with the Control group ($p < 0.05$). No benefit was observed for any parameter in the Resting group as compared withthose parameters
in the CG group ($p < 0.05$). We observed a lower fibrosis score and less peritoneal thickness in the GC group as compared with the Resting group ($p < 0.05$). No beneficial effects of AZT on peritoneal morphology were observed as compared with the effects of peritoneal rest or corticosteroid therapy. Treatment with cyclosporin resulted in more fibrosis, vascularity, and inflammation than was seen with
corticosteroid therapy ($p < 0.05$). Immunosuppressive therapies, especially those that are corticosteroid-based, may have therapeutic value in the management of EPS. Patients treated with cyclosporin may have a risk for developing EPS.

# Induzione della fibrosi peritoneale con CNI: esperienza clinica

in tutti i casi descritti di EPS post-Tx l'immunosoppressione si basa sui CNI

# Inibizione della fibrosi peritoneale con mTOR-I: meccanismi

El-Hashemite N et al: Loss of Tsc1 or Tsc2 induces Vascular Endothelial Growth Factor production through Mammalial Target of Rapamicin. Cancer Research 2003;63:5173-5177

Martinet W et al: Everolimus triggers cytokine release by macrophages. Arterioscler Thromb Vasc Biol 2012; DOI: 10.1161/AT VBAHA.112.245381

Sekigushi Y et al: Rapamycin inhibits transforming growth factor β-induced peritoneal angiogenesis by blocking the secondary hypoxic response. J Cell Mol Med 2012;8:1934-1945

Gonzalez-Mateo GT et al: Rapamycin protects from type-I peritoneal membrane failure inhibiting the angiogenesis, lymphangiogenesis, and endo-MT. BioMed Research Int 2015;Article ID 989560

Xiang S et al: Rapamycin inhibits epithelial-to-mesenchymal transition of peritoneal mesothelium cells through regulation of Rho GTPases. FEBS J 2016;283:1309-2325

Liu J et al: Mammalian target of rapamycin complex 1 activation disrupts the low-density lipoprotein receptor pathway: a novel mechanism for extracellular matrix accumulation in human peritoneal mesothelial cells. Am J Nephrol 2018;48:357-368

Liu J et al: Rapamycin inhibits peritoneal fibrosis by modifying lipid homeostasis in the peritoneum. Am J Transl Res 2019;11:1473-1485

Xu T et al: Comparison of anti-peritoneal fibrotic effects between an mTORC1-specific blocker and a PI3K/mTOR dual-blocker. Renal Failure 2019;41:267-277

Lu H et al: Molecular hydrogen regulates PTEN-AKT-mTOR signaling via ROS to alleviate peritoneal dialysis-related peritoneal fibrosis. FASEB J 2020;34:4134-4146

# Inibizione della fibrosi peritoneale con mTOR-I: studi in colture cellulari

Aguilera A et al: Effects of rapamycin on the epithelial-to-mesenchymal transition on human peritoneal mesothelial cells. Int J Artif Organs 2005;28:164-169

Xiang S et al: Rapamycin inhibits epithelial-to-mesenchymal transition of peritoneal mesothelium cells through regulation of Rho GTPases. FEBS J 2016;283:1309-2325

# Inibizione della fibrosi peritoneale con mTOR-I: studi su modelli animali

Duman S et al: Effects of everolimus as an antiproliferative agent on regression of encapsulating peritoneal sclerosis in a rat model. Adv Perit Dial 2008;24:104-110

Patsenker E et al: Potent antifibrotic activity of mTOR inhibitors sirolimus and everolimus but not a cyclosporine A and tacrolimus in experimental liver fibrosis. J Hepatol 2011;55:388-398

Ceri M et al: Effect of sirolimus on the regression of peritoneal sclerosis in an experimental rat model. Int Urol Nephrol 2012;44:977-982

Xu T et al: Impact of rapamycin on peritoneal fibrosis and transport function. Blood Purif 2012;34:48-57

Sagiroglu T et al: Comparison of sirolimus and colchicine treatment on the development of peritoneal fibrosis in rats having peritoneal dialysis.  Balkan Med 2015;32:101-106

Acikgoz-Mert GS et al: Effect of bevacizumab and everolimus combination treatment on peritoneal sclerosis in an experimental rat model. Ther Apher Dial 2021;25:323-330

# mTOR-I nella terapia dell'EPS: studi clinici

da Silva N et al: Post-transplantation encapsulating peritoneal sclerosis in a pediatric patient. Pediatr Nephrol 2012;27:1583-1588

Huddam U et al: Additive effectiveness of everolimus plus tamoxifen therapy in treatment of encapsulating peritoneal sclerosis. Renal Failure 2012;34:387-389

Frascà GM et al: m-TOR inhibitors may be useful in the treatment of encapsulating peritoneal sclerosis (EPS). J Nephrol 2014 DOI 10.1007/s40620-014-0052-5

Romagnoli J et al: Posttransplant  encapsulating peritoneal sclerosis, long-term success with everolimus and low-dose CNI: a case report. Transplant Proc 2014;46:2368-2370

Sud R et al: A role for everolimus in post-transplant encapsulating peritoneal sclerosis: first case report. Nephrology (Carlton) 2014; DOI 10.1111/nep.12196

Messina M et al: mTOR inhibitors for medical treatment of post-transplantation encapsulating peritoneal sclerosis: a favourable single-center experience. J Nephrol 2015;28:245-249

RENAL FAILURE, 2016 http://dx.doi.org/10.1080/0886022X.2016.1209026

# mTOR inhibitors for management of encapsulating peritoneal sclerosis: a review of literatures

Maryam Ghadimi[a], Simin Dashti-Khavidaki[b,c] and Hossein Khalili[c]

Method: Thirteen case reports/series consisted of 20 patients (16 post-transplant and four post-hemodialysis EPS cases) were evaluated. We tried to extract the effect of mTOR inhibitors according to authors' conclusion and the time of improvement of patients' symptoms and each treatment modality such as surgery, parenteral nutrition, tamoxifen and mTOR inhibitors.

Results: Of 20 patients, clinical improvement of five patients (25%) is more attributable to mTOR inhibitor therapy. All these five patients were post-kidney transplant EPS cases. Therefore, EPS improvement rate in post-transplant EPS patients was 31.25% (5 of 16 patients). Death after EPS diagnosis occurred in two of seven patients with continued CNIs therapy (28.57%) and 1 of 11 cases (9.09%) who didn't receive CNIs after EPS diagnosis.

Conclusion: Although the therapeutic effect of mTOR inhibitors against EPS remains unproven, it seems that for patients with post kidney transplant EPS who do not have any contraindication for mTOR inhibitor administration, converting from CNIs to mTOR inhibitors in addition to other EPS treatments may result in improving EPS in approximately one-third of patients and decreasing patients' mortality.

# Additive Effectiveness of Everolimus Plus Tamoxifen Therapy in Treatment of Encapsulating Peritoneal Sclerosis

Bülent Huddam[1], Alper Azak[1], Gülay Koçak[1], Murat Başaran[1], Nuray Voyvoda[2] and Murat Duranay[1]

*Renal Failure*, 34(3): 387–389, (2012)

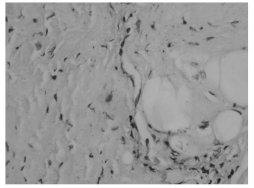


Figure 2. Peritoneal membrane biopsy showing extended fibrosis.

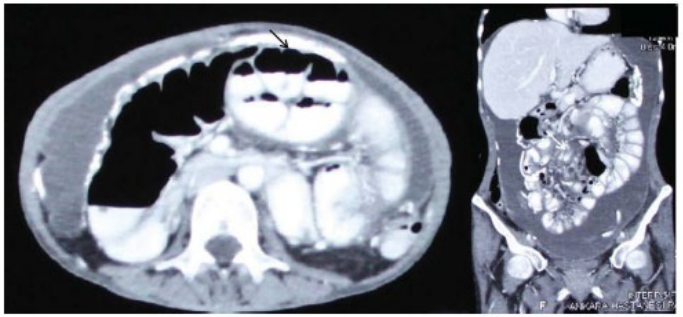


Figure 1. CT scan of lower abdomen shows clustered gas-containing small-bowel loops with thick membrane-like sac (white arrow) and dilated proximal small bowel with air–fluid levels (black arrow) due to intestinal obstruction.

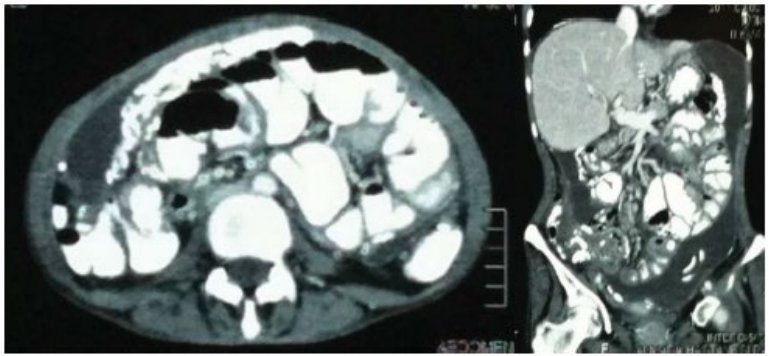
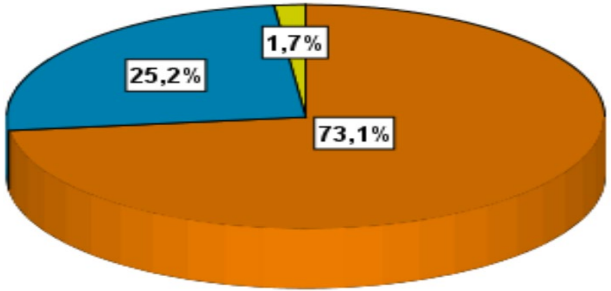


Figure 3. Control examination after 2 months of drug treatment: the clustered small-bowel loop has disappeared.

Peritoneal dialysis (PD) is one of the commonly used choices of continuous renal replacement therapies. Peritoneal membrane is damaged by using solutions with lower biocompatibility, peritonitis episodes, and vintage of PD therapy. Encapsulating peritoneal sclerosis (EPS) is a rare complication of PD and is presented by progressive fibrosis of the peritoneum. Fibrous tissue entrapment of the intestine, leading to complete intestinal obstruction, is referred to as EPS, the most severe form of sclerosing peritonitis. EPS is irreversible fibrosis of the peritoneal membrane usually associated with high rates of morbidity and mortality. Preventive strategies are the best choice of treatment. Also there is no proven effective therapy for EPS; there are only small-sized trials. Herein we present a case of EPS who improved with everolimus plus tamoxifen therapy.

# Terapia: CNI, mTOR-I




**i casi di EPS si concentrano in chi fa solo CNI senza mTOR-I con una significatività elevatissima**

# Terapia: CNI, mTOR-I vs diagnosi di EPS

**Tavola di contingenza Terapia * Diagnosi EPS**

| | | | Diagnosi EPS | | |
|---|---|---|---|---|---|
| | | | No | Si | Totale |
| Terapia | Inibitori della calcineurina | Conteggio | 1166 | 34 | 1200 |
| | | % in Terapia | 97,2% | 2,8% | 100,0% |
| | | % in Diagnosi EPS | 72,6% | 97,1% | 73,1% |
| | Inibitori della calcineurina + MTOR | Conteggio | 413 | 1 | 414 |
| | | % in Terapia | 99,8% | 0,2% | 100,0% |
| | | % in Diagnosi EPS | 25,7% | 2,9% | 25,2% |
| | mTOR inibitori | Conteggio | 28 | 0 | 28 |
| | | % in Terapia | 100,0% | 0,0% | 100,0% |
| | | % in Diagnosi EPS | 1,7% | 0,0% | 1,7% |
| Totale | | Conteggio | 1607 | 35 | 1642 |
| | | % in Terapia | 97,9% | 2,1% | 100,0% |
| | | % in Diagnosi EPS | 100,0% | 100,0% | 100,0% |

**Test del chi-quadrato**

| | Valore | gl | Sign. asint. |
|---|---|---|---|
| Chi-quadrato di Pearson | 10,532[a] | 2 | ,005 |
| Rapporto di verosimiglianza | 15,222 | 2 | ,000 |
| N di casi validi | 1642 | | |

a. 1 celle (16,7%) hanno un conteggio previsto inferiore a 5. Il conteggio previsto minimo è ,60.

# Come calcolare la probabilità di EPS all'atto del trapianto

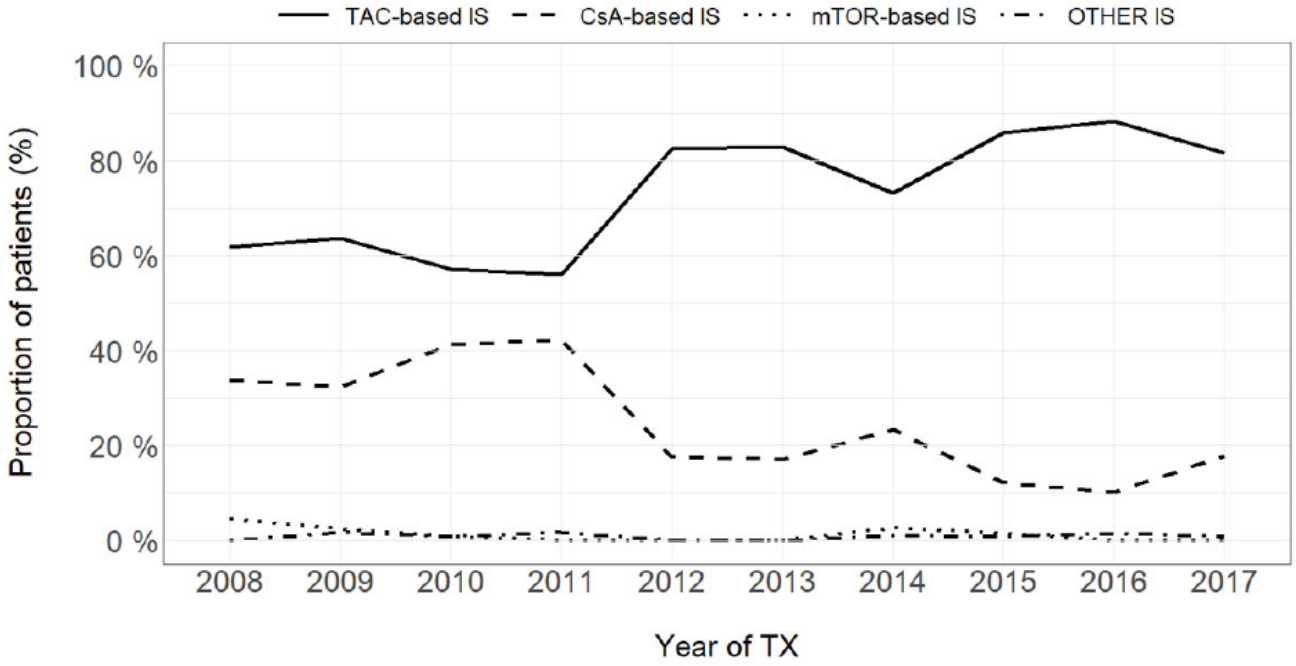
| Anni di dialisi peritoneale | Probabilità di EPS con solo CNI | Probabilità di EPS con CNI+mTOR |
|---|---|---|
| 1 | 1,09% | 0,10% |
| 2 | 1,40% | 0,13% |
| 3 | 1,78% | 0,17% |
| 4 | 2,27% | 0,22% |
| 5 | 2,89% | 0,28% |
| 6 | 3,68% | 0,35% |
| 7 | 4,66% | 0,45% |
| 8 | 5,90% | 0,58% |
| 9 | 7,43% | 0,74% |
| 10 | 9,33% | 0,95% |

Immunosuppression management in renal transplant recipients with normal-immunological risk: 10-year results from the Swiss Transplant Cohort Study

Swiss Med Wkly. 2020;150:w20354

Krisl Andreas[a], Stampf Susanne[ab], Hauri Dimitri[b], Binet Isabelle[bc], Mueller Thomas[bd], Sidler Daniel[be], Hadaya Karine[bf], Golshayan Déla[bg], Pascual Manuel[bg], Koller Michael[ab*], Dickenmann Michael[ab*], the Swiss Transplant Cohort Study (STCS)

**Figure 1:** Illustration of time trends for the prescription of different immunosuppressive (IS) regimens in normal-risk renal transplant (TX) recipients between 2008 and 2017."TAC-based" was defined as the combination of prednisone, tacrolimus and mycophenolate mofetil. "CsA-based" corresponds to the combination of ciclosporin, prednisone and mycophenolate mofetil. "mTOR-based" corresponds to the combination of any calcineurin inhibitor, everolimus and prednisone, with or without mycophenolate mofetil. All other immunosuppressive drug combinations and therapies were summarised as "Other" immunosuppression.




EPS post-Tx:

- indotta dai CNI (tacrolimus, ciclosporina)
- prevenuta e curata dagli mTOR-I (sirolimus, everolimus)
- belatacept (probabilmente ininfluente sulla EPS) registrato in Italia in classe C

Nephrol Dial Transplant (2023) 38: 2170–2181

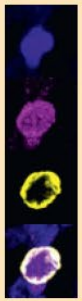
# Peritoneal transformation shortly after kidney transplantation in pediatric patients with preceding chronic peritoneal dialysis

Conghui Zhang[1], Maria Bartosova[1], Iva Marinovic[1], Constantin Schwab[2], Betti Schaefer[1], Karel Vondrak[3], Gema Ariceta[4], Ariane Zaloszyc[5], Bruno Ranchin[6], Christina Taylan[7], Rainer Büscher[8], Jun Oh[9], Arianeb Mehrabi[10] and Claus Peter Schmitt[1]

## Methods

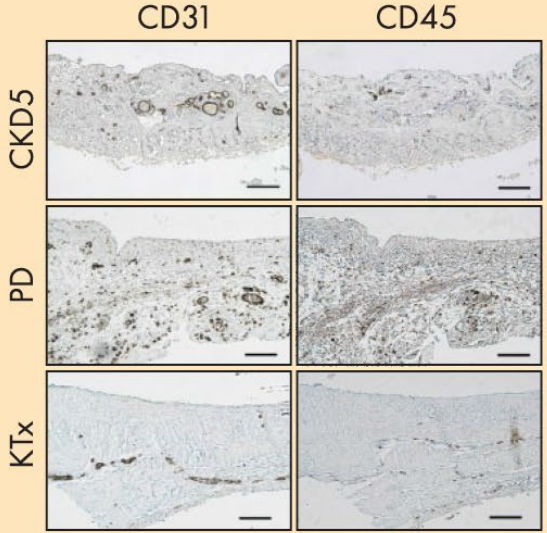
**Peritoneal tissues from children:**

- CKD5 (n=81)
- Low-GDP PD (n=72)
- 4–8 weeks post KTx with preceding low-GDP PD (n=20)
- Matched subgroup validation



- Digital histomorphometry
- Quantitative immunohistochemistry
- Confocal microscopy

## Results




**Peritoneum after KTx:**

| | |
|---|---|
| **Microvessel density** (CD31) | ✓ Similar to CKD5<br>Halved versus PD |
| **Leucocyte infiltration** (CD45) | ✓ Halved versus PD |
| **Vessel maturation** (HIF-1a, angiopoetin1/2) | ✓ Improved vs. PD |

**But:**

- Persistent mesothelial loss and profibrotic activity
- Diffuse podoplanin positivity (40%)
- High vascular senescence and apoptosis markers

Peritoneal inflammation is less severe in patients after KTx, while mesothelial denudation, diffuse podoplanin positivity and profibrotic activity are prevalent, the latter possibly due to the impact of CNI.

G Ital Nefrol 2023 - ISSN 1724-5990 - © 2023 Società Italiana di Nefrologia – Anno 40 Volume 3 n° 2

# Encapsulating Peritoneal Sclerosis – Comment on the 8th GPDP-SIN 2022 Census data

Guido Garosi[1], Nicoletta Mancianti[1]

The reduction in the incidence of EPS in PD in Italy is a real phenomenon, and in keeping with data reported internationally. The main determinant is shown to be the corresponding fall in peritonitis, with the reduced glucose load and the use of more biocompatible dialysis solutions also very likely to be playing a role. The monitoring by all Centers of ultrafiltration and patient peritoneal transport characteristics is strongly to be recommended, while the incongruity of an a priori limitation of the duration of PD is confirmed.

The failure to document cases of post-Tx EPS, whose incidence is constant in international reports, seems on the other hand to be secondary to the inadequacy on the part of the Census to intercept them, which is in turn due to both a lack of Transplant Center awareness of EPS issues and the organizational separation between Transplant Centers and PD teams. A deficit in reporting is also likely with regard to EPS in HD, the rarest of all, linked to a lack of collaboration between PD and HD personnel. The take-home message is: we are achieving good results with EPS in PD, but the battle is not over yet and we have to continue to prevent, diagnose and treat it.

# Casi di EPS che guariscono dopo trapianto con steroidi ad alte dosi

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# Studi prospettici confermano che gli steroidi possono essere efficaci nell'EPS

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Kawanishi H et al: Encapsulating peritoneal sclerosis in Japan: A prospective, controlled, multicenter study. Am J Kidney Dis 2004;44:729-37

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*American Journal of Kidney Diseases*, Vol 44, No 4 (October), 2004: pp 729-737

# Encapsulating Peritoneal Sclerosis in Japan: A Prospective, Controlled, Multicenter Study

Hideki Kawanishi, MD, Yoshindo Kawaguchi, MD, Hiroyoshi Fukui, MD, Shigeko Hara, MD, Akio Imada, MD, Hitoshi Kubo, MD, Masao Kin, MD, Masahiko Nakamoto, MD, Seiji Ohira, MD, and Takao Shoji, MD, for the Long-Term Peritoneal Dialysis Study Group

**Table 2. Incidence and Outcome of EPS in Relation to Time on PD**

| PD Duration (y) | Number of Patients | EPS Cases (Incident Rate %) | Mortality (%) | Recovery (%) |
|---|---|---|---|---|
| <3 | 337 | 0 | — | — |
| 3 to <5 | 554 | 4 (0.7) | 0 (0) | 4 (100) |
| 5 to <8 | 576 | 12 (2.1) | 1 (8.3) | 10 (83.3) |
| 8 to <10 | 239 | 14 (5.9) | 4 (28.6) | 6 (42.9) |
| 10 to 15 | 223 | 13 (5.8) | 8 (61.5) | 2 (15.3) |
| >15 | 29 | 5 (17.2) | 5 (100) | 0 (0) |
| Total | 1,958 | 48 (2.5) | 18 (37.5) | 22 (45.8) |

**Table 3. The Therapeutic Methods and Outcomes**

| Therapeutic Method | Patients | Recovery (%) | Recovery Cases (PD Duration [mo]*) | Nonrecovery Cases (PD Duration [mo]*) | *P*† |
|---|---|---|---|---|---|
| TPN only | 3 | 0 (0) | | 151.4 ± 25.1 | NA |
| Corticosteroids‡ | 39 | 15 (38.5) | 79.2 ± 29.3 | 136.7 ± 39.7 | <0.001 |
| Surgery§ | 12 | 7 (58.3) | 95.7 ± 32.5 | 105.5 ± 23.1 | NS |

Abbreviations: NA, not applicable; NS, not significant.
*PD duration at EPS onset.
†PD duration for recovery *v* nonrecovery cases.
‡Twenty-seven patients also treated with TPN, and 6 patients with steroid + surgery + TPN.
§All patients also treated with TPN.

# EPS: terapia farmacologica (in associazione!)

Prednisone per os 0.5 mg/kg/die 8-12 settimane, quindi tapering

Tamoxifene per os 10-20 mg/die a tempo indefinito

mTOR-I a tempo indefinito:
Sirolimus (livello ematico ≈ 6 ng/ml)
oppure Everolimus (livello ematico ≈ 3 ng/ml)

Terapia ipertensione con ACE-I o ARB, preferibilmente no β-bloccanti

EPS post-TX: shift da CNI a mTOR-I (basso rischio immunologico)
shift da CNI a CNI + MTOR-I (alto rischio immunologico)


Kidney Blood Press Res 2022;47:125–134

# Peritoneal Expression of SGLT-2, GLUT1, and GLUT3 in Peritoneal Dialysis Patients

Severin Schricker[a] Tina Oberacker[b] Peter Fritz[a] Markus Ketteler[a]
Mark Dominik Alscher[a] Moritz Schanz[a]

**Table 2.** Clinical data of study patients

| Variable | Control | Uremic | PD <12 months | PD >12 months | EPS |
|---|---|---|---|---|---|
| *N* | 8 | 11 | 18 | 23 | 12 |
| Age, years | | | | | |
| Median | 64.5 | 65.0 | 64.0 | 62.0 | 51.5 |
| IQR | 55.5–70.8 | 49.0–75.0 | 53.0–69.3 | 46.0–71.0 | 45.3–58.8 |
| Female/male | 6/2 | 3/8 | 4/14 | 9/14 | 3/9 |
| PD duration, months | | | | | |
| Median | | | 10.5 | 44.0 | 70.0 |
| IQR | | | 6.0–11.25 | 29.0–52.0 | 55.5–99.5 |
| Diabetes, *n* (%) | 1 (13) | 3 (27) | 8 (44) | 8 (35) | 0 (0) |
| Hypertension, *n* (%) | 1 (13) | 9 (82) | 14 (78) | 23 (100) | 11 (92) |
| Smokers, *n* (%) | 1 (13) | 3 (27) | 7 (39) | 8 (35) | 2 (17) |

Percentages are rounded to whole numbers. EPS, encapsulating peritoneal sclerosis; IQR, interquartile range; *n*, number of values; PD, peritoneal dialysis.

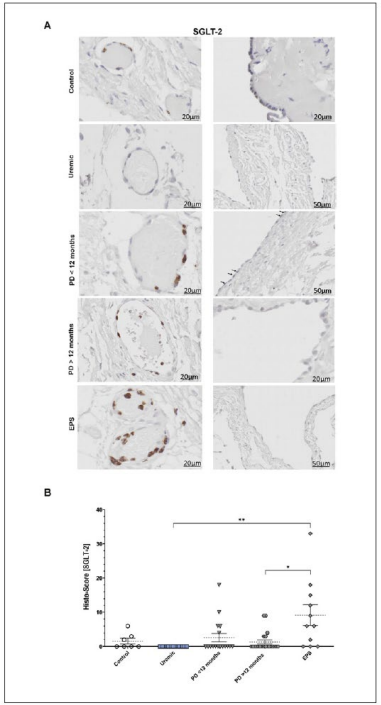


**Fig. 2.** Expression and localization of SGLT-2 in the human peritoneum. **A** Representative peritoneal sections stained for SGLT-2. For each subgroup, a section showing vessels (first row) and mesothelium (second row) is shown. Arrows are indicating very weak staining of few mesothelial cells. **B** Scatter plots show the Histo-Score of the immunohistochemical sections. Negative staining was obtained in 46 out of 67 sections. Statistical differences were determined by a Kruskal-Wallis test and Dunn's post hoc analysis (mean ± SEM; ns, not significant; $^{**}p < 0.01$, $^{*}p < 0.05$; control: $n = 7$, uremic: $n = 11$, PD <12 months: $n = 17$, PD >12 months: $n = 21$, and EPS: $n = 11$). EPS, encapsulating peritoneal sclerosis.

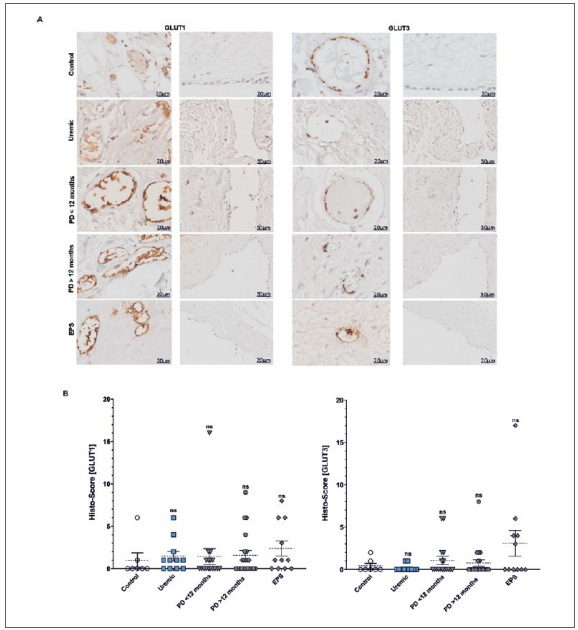


**Fig. 3.** Expression and localization of GLUTs in the human peritoneum. **A** Representative peritoneal sections of vessels (first and third row) and of mesothelium (second and fourth row) stained for GLUT1 (left panels) and GLUT3 (right panels). **B** Scatter plots show the Histo-Score of all immunohistochemical sections. Negative staining was obtained in 34 out of 67 sections for GLUT1 and 46 out of 67 sections for GLUT3. Statistical differences were determined by Kruskal-Wallis test and Dunn's post hoc analysis (mean ± SEM; ns, not significant; control: $n = 7$, uremic: $n = 11$, PD <12 months: $n = 17$, PD >12 months: $n = 21$, and EPS: $n = 11$). EPS, encapsulating peritoneal sclerosis.

Peritoneal biopsies of patients (healthy controls, uremic, PD, and encapsulating peritoneal sclerosis [EPS]) were analyzed. We found evidence of SGLT-2, GLUT1, and GLUT3 expression in the peritoneal membrane. Protein expression of SGLT-2 increases with PD duration and is significantly enhanced in EPS patients. All transporters were predominantly, but not exclusively, located adjacent to the vessel walls of the peritoneal membrane.

# Canagliflozin alleviates high glucose-induced peritoneal fibrosis via HIF-1α inhibition

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Frontiers in Pharmacology
PUBLISHED 11 May 2023
DOI 10.3389/fphar.2023.1152611

We investigated the peritoneal protective mechanisms of Canagliflozin in vitro by simulating hypoxia with CoCl2 in human peritoneal mesothelial cells (HPMCs) and rats by intraperitoneal injection of 4.25% peritoneal dialysate simulating chronic high glucose exposure. CoCl2 hypoxic intervention significantly increased HIF-1α abundance in HPMCs, activated TGF-β/p-Smad3 signaling, and promoted the production of fibrotic proteins (Fibronectin, COL1A2, and α-SMA). Meanwhile, Canagliflozin significantly improved the hypoxia of HPMCs, decreased HIF-1α abundance, inhibited TGF-β/p-Smad3 signaling, and decreased the expression of fibrotic proteins. Five-week intraperitoneal injection of 4.25% peritoneal dialysate remarkably increased peritoneal HIF-1α/TGF-β/p-Smad3 signaling and promoted peritoneal fibrosis and peritoneal thickening. At the same time, Canagliflozin significantly inhibited the HIF-1α/TGF-β/p-Smad3 signaling, prevented peritoneal fibrosis and peritoneal thickening, and improved peritoneal transportation and ultrafiltration. High glucose peritoneal dialysate increased the expression of peritoneal GLUT1, GLUT3 and SGLT2, all of which were inhibited by Canagliflozin. In conclusion, we showed that Canagliflozin could improve peritoneal fibrosis and function by ameliorating peritoneal hypoxia and inhibiting the HIF-1α/TGF-β/p-Smad3 signaling pathway, providing theoretical support for the clinical use of SGLT2 inhibitors in patients on peritoneal dialysis.

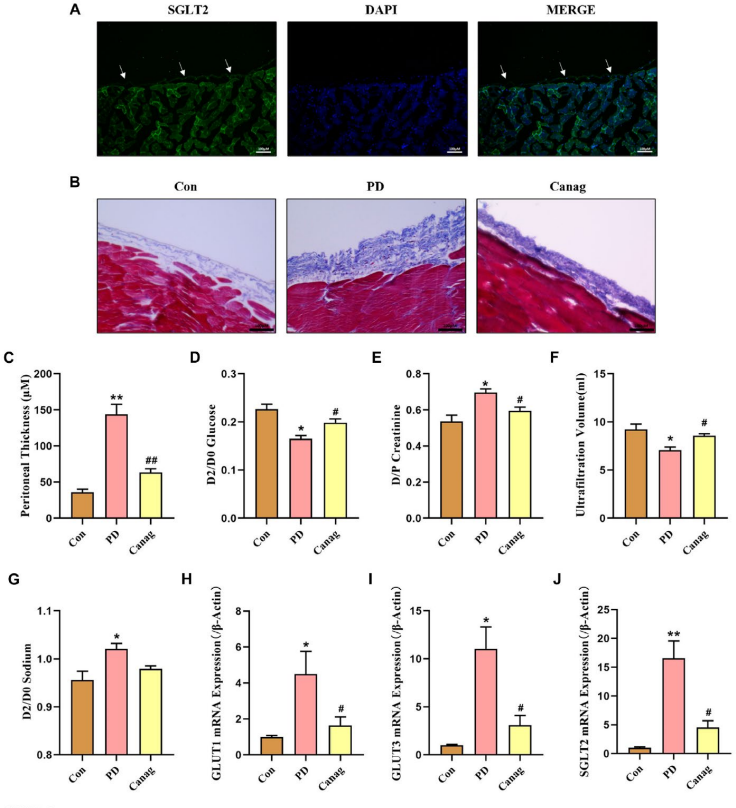


FIGURE 4
Canagliflozin prevents peritoneal -thickness and improves peritoneal function in rats. **(A)** Immunofluorescence detection of SGLT2 expression in the peritoneal membrane. **(B)** Masson trichrome staining of rat peritoneal membrane in different groups. **(C)** Thickness quantitative analysis of the rat peritoneum in each group. **(D–G)** Peritoneal function based on glucose absorption (glucose concentration ratio of 2 and 0-h peritoneal dialysate, D2/D0), creatinine transportation (creatinine concentration ratio of 2-h peritoneal dialysate and plasma, D/P), ultrafiltration and sodium transportation (sodium concentration ratio of 2 and 0-h peritoneal dialysate, D2/D0) in each group of rats. **(H–J)** Peritoneal mRNA expressions of GLUT1, GLUT3 and SGLT2 detected by real-time quantitative PCR. *, $p < 0.05$; **, $p < 0.001$ vs Con group. #, $p < 0.05$; ##, $p < 0.001$ vs PD group.


# Dapagliflozin in peritoneal dialysis patients: a pilot study evaluating peritoneal membrane function

*BMC Nephrology* (2024) 25:37

Zakaria Hamdan[1*], Yusri Abdel-Hafez[2], Ahmad Enaya[1], Alaa Sarsour[3], Lubna Kharraz[4] and Zaher Nazzal[5*]

Background: Patients taking SGLT-2 inhibitors may experience delayed peritoneal fibrosis, better ultrafiltration of water and toxins, and higher survival rates. We aimed to evaluate the possible effects of Dapagliflozin in changing the peritoneal solute transfer rate, reducing peritoneal glucose absorption, and, hence, increasing ultrafiltration.
Methodology: A pilot pre-post interventional study was used to evaluate 20 patients on continuous ambulatory peritoneal dialysis (CAPD) enrolled in a one-month self-controlled study [Trial#: NCT04923295]. Inclusion criteria included being over 18, and having a Peritoneal Dialysis (PD) vintage of at least six months. All participants were classified as having high or average high transport status based on their Peritoneal Equilibrium Test with a D0/D4 > 0.39 and using at least two exchanges with 2.35% dextrose over the previous three months before enrollment.
Results: Following the treatment, 13 patients had an increase in median D4/D0 from 0.26 [0.17–0.38] to 0.31 [0.23–0.40], while seven patients had a decline from 0.28 [0.17–0.38] to 0.23 [0.14–0.33]. Additionally, nine patients had a decrease in median D/P from 0.88 [0.67–0.92] to 0.81 [0.54–0.85], while 11 patients had an increase from 0.70 [0.6–0.83] to 0.76 [0.63–0.91].
Conclusion: According to the findings of this study, Dapagliflozin usage in peritoneal dialysis patients did not result in a reduction in glucose absorption across the peritoneal membrane. Additionally, Dapagliflozin was also associated with a small increase in sodium dip, a decrease in peritoneal VEGF, and a decrease in systemic IL-6 levels all of which were not statistically significant. Further large-scale studies are required to corroborate these conclusions.

Med Sci Monit, 2019; 25: 3566-3572

# Comparison of the Effects of Indobufen and Warfarin in a Rat Model of Adenine-Induced Chronic Kidney Disease

Xiaowei Lou
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Jianguang Gong
Li Zhao
Yiwen Li*
Qiang He*

Background: Worldwide, the treatment of patients with chronic kidney disease (CKD) remains a challenge as warfarin treatment can be associated with severe adverse events related to bleeding. Alternative anticoagulants that can be used in CKD remain to be identified. This study aimed to compare the effects of indobufen, a new antiplatelet agent, with warfarin in a rat model of adenine-induced CKD.

Material/Methods: Forty-eight male Wistar rats were treated with intragastric adenine to create the rat model of CKD and were divided into four groups: an untreated control group (N=12), a group treated with dimethyl sulfoxide (DMSO) (N=12), a group treated with indobufen, (N=12) and a group treated with warfarin (N-12). Treatment was given for 4 weeks and 8 weeks. Kidney histology was performed, and the degree of fibrosis was quantified using Masson trichrome staining.

Results: In the rat model of adenine-induced CKD, Masson trichrome staining showed that the degree of kidney fibrosis in the indobufen group (26%) was significantly reduced ($p<0.05$) when compared the DMSO group (58%) and the warfarin group (49%). Kidney fibrosis was associated with upregulation of 6-keto-PGI2/TXB2 in the rat kidney tissue.

Conclusions: In a rat model of adenine-induced CKD, preliminary findings showed that indobufen was associated with reduced kidney fibrosis when compared with warfarin.

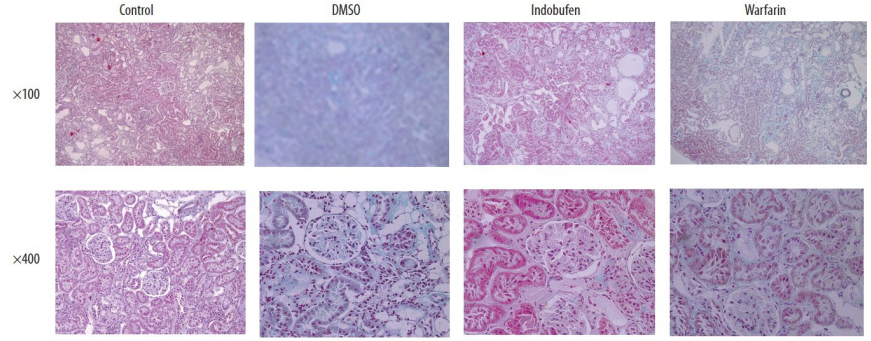


**Figure 4.** Photomicrographs of the histology of the kidneys in the rat model of adenine-induced chronic kidney disease (CKD) in the control group and rats treated with dimethyl sulfoxide (DMSO), indobufen, and warfarin. Masson trichrome and hematoxylin and eosin (H&E). Magnification: ×100, and ×400.

**Table 1.** The proportion of the kidney tissue showing staining with Masson trichrome for fibrosis in the rat model of adenine-induced chronic kidney disease (CKD) in the control group and rats treated with dimethyl sulfoxide (DMSO), indobufen, and warfarin.

| Treatment group | Control | DMSO | Indobufen | Warfarin |
|---|---|---|---|---|
| Area stained with Masson trichrome | 0% | 58% | 26% | 49% |

For each group, three random fields were chosen and the percentage of the stained area in the total field was measured using ImageJ software. The results represent the average percentage.


J Pharmacol Exp Ther 384:296–305, February 2023

# The Effects of Indobufen on Micro-Inflammation and Peritoneal Transport Function in Patients Undergoing Continuous Ambulate Peritoneal Dialysis: A Prospective Randomized Controlled Study

Fang Liu,[1] Hao Zhang,[1] Hong Wu, Shikun Yang, Jun Liu, and Jianwen Wang

ABSTRACT

Indobufen possesses anticoagulant and antithrombotic effects that can improve micro-inflammation and renal function. This study aimed to examine whether indobufen could improve the microinflammatory state in patients on continuous ambulatory peritoneal dialysis (CAPD) and explore its therapeutic effects on peritoneal transport function. A total of 60 patients undergoing CAPD from October 2019 to October 2020 were selected and randomized to the control and indobufen groups. All patients received conventional treatments. Blood routine and the serum and peritoneal effusion levels of tumor necrosis factor-a (TNF-a), transforming growth factor-b1 (TGF-b1), cellular fibronectin (cFN), and vascular endothelial growth factor were determined before and after 6 months of treatment. The peritoneal equilibrium test (PET) was used to evaluate peritoneal transport function. There were no significant differences in PET results, microinflammatory state, and biochemical indices between the two groups before treatment ($P > 0.05$). After 6 months of treatment, platelet-tolymphocyte ratio and serum and peritoneal effusion TNF-a levels in the indobufen group were decreased compared with the control group ($P < 0.05$). Serum and peritoneal effusion TGF-b1 and cFN levels in the indobufen group were reduced compared with the control group ($P < 0.05$). PET results in the indobufen group were decreased compared with baseline ($P < 0.05$). The difference in PET results between the two groups before and after treatment was statistically significant ($P < 0.05$). Indobufen could improve the peritoneal transport function in patients undergoing CAPD. The underlying mechanismmight be related to the improvement of the microinflammatory state and peritoneal fibrosis.

SIGNIFICANCE STATEMENT

Microinflammation and peritoneal fibrosis can lead to peritoneal failure in CAPD. Indobufen is a novel antiplatelet drug that can alleviate renal fibrosis and improve renal function in patients with diabetic nephropathy. Indobufen can improve the peritoneal transport function in patients undergoing CAPD. The mechanism of indobufen improving the peritoneal function might be related to the improvement of the microinflammatory state and peritoneal fibrosis.