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Corresponding Author	Family Name	**Goffin**
	Particle	
	Given Name	**E. J.**
	Suffix	
	Division/Department	Nephrology
	Organization/University	Cliniques Universitaires Saint-Luc
	City	Brussels
	Country	Belgium
	Email	eric.goffin@uclouvain.be
Author	Family Name	**Krediet**
	Particle	
	Given Name	**R. T.**
	Suffix	
	Division/Department	Nephrology
	Organization/University	Amsterdamumc
	City	Amsterdam
	Country	The Netherlands AU1
	Email	R.T.Krediet@amc.uva.nl r.t.krediet@amsterdamumc.nl
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Encapsulating Peritoneal Sclerosis

E. J. Goffin and R. T. Krediet

Contents

Abstract

Encapsulating peritoneal sclerosis (EPS) is the most serious complication of long-term PD. In this chapter a review will be given on risk factors, EPS epidemiology, its pathology, pathogenesis, clinical manifestations, investigations, treatment, and prevention.

Keywords

Encapsulating peritoneal sclerosis · Peritoneal dialysis · Long-term peritoneal abnormalities · Biocompatibility

Encapsulating peritoneal sclerosis (EPS) is a rare, excessive fibrogenic reaction of the peritoneal membrane that leads to extensive peritoneal sclerosis, bowel adhesions, and recurrent intestinal obstruction episodes. In most severe cases, bowel loops become totally encapsulated in a fibrotic cocoon responsible of intestinal occlusions, malnutrition, sepsis, and death [1–4]. Though this entity affects a minority of patients on peritoneal dialysis (PD) ranging from 0.9% to 3.5%, it constitutes its most severe and devastating complication with reported mortality rates as high as 50% [2].

E. J. Goffin (✉)
Nephrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium
e-mail: eric.goffin@uclouvain.be

R. T. Krediet
Nephrology, Amsterdamumc, Amsterdam, The Netherlands
e-mail: R.T.Krediet@amc.uva.nl
r.t.krediet@amsterdamumc.nl

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Risk Factors

EPS is a multifactorial condition of unknown origin that has been described in association with, or as a consequence of, various pathological conditions, like intra-abdominal neoplasias, liver cirrhosis, hepatic transplantation, auto-immune disorders, and peritoneal tuberculosis [5]. PD duration is probably the most important risk factor in PD patients: EPS has rarely been reported to occur before 3 years on PD and its prevalence progressively increases with the duration of PD [1, 2, 6–9]. Other conditions associated with EPS development in PD patients have been summarized extensively in [10] and include the following items: (1) chlorhexidine, which was used in the 1980s as chemical antiseptic agent to sterilize tubing connections; (2) cumulative glucose exposure and the use of bioincompatible PD fluids; (3) younger age, probably as the consequence of a lower competing risk of death and/or because younger patients have highly active repair capacity of damaged tissue; (4) peritonitis episodes, although a number of studies failed to show this [9, 11, 12], and EPS has been described in patients without any peritonitis episode; (5) β-blockers such as practolol in the 1970s, and immunosuppressive pro-fibrotic agents, like calcineurin inhibitors. The latter have been shown to induce peritoneal fibrosis in a rat model [13] and also when given in renal transplant recipients [2]. In up to 50% of cases, EPS develops or symptomatically progresses after PD discontinuation [1, 2, 8, 14]. Although the clinical manifestations are often less severe, it contributes to the mortality in patients with a kidney transplant [15].

Epidemiology of EPS

Initially based on local case-report descriptions or on short series from various centers [16, 17], EPS epidemiology currently relies on multicenter or national registry cohorts [7, 8, 18]. Most of current knowledge comes from Japanese patients, probably because they often remain on PD for long durations [6]. Kawanishi et al. reported an EPS incidence of 0.7% after 5 years, 2.1% after 8 years, 5.9% after 10 years, and 17.2% after 15 years on PD, respectively [6]. EPS occurred in 33 out of 7618 patients from the ANZDATA registry, in which patients have been assessed across 4 consecutive periods, ranging from 1995 to 2007, giving an incidence of 1.8 per 1000 patient-years. Cumulative incidences at 3, 5, and 8 years were 0.3, 0.8 and 3.9%, respectively [1]. A progressive increase in the cumulative risk of developing EPS was found in the Scottish Registry after 3.5 years since the first exposure to PD, reaching a cumulative incidence of 8.1% at 8 years [7]. Noteworthy, 11% of the EPS cases reported in the Pan-Thames EPS study occurred in patients who had been on PD for less than 3 years [19]. An explanation might be that the diagnosis was largely based on CT scans, interpreted by various radiologists. Altogether, the reported prevalence of EPS varies between 0.4% and 8.9%, the incidence rate between 0.7 and 13.6 per 1000 patient-years, and the risk of occurrence after 5 years on PD between 0.6 and 6.6% [reviewed in 8]. The variability observed among EPS incidence worldwide could be accounted for by still-unknown individual genetic polymorphism predispositions in pro-fibrotic genes, local differences in microorganisms causing peritonitis, and/or in PD management, for instance the glucose3 load or the use of biocompatible PD fluids. It is remarkable in this context that no single EPS case had been reported to the ANZDATA Registry between 2004 and 2007; an observation ascribed to the systematic use of biocompatible dialysis fluids [1]. Alternatively, methodological biases, such as inadequate reporting or lead time biases regarding PD exposure, could explain why EPS incidence is so variable in the different studies [8]. More recent data support the Australian and New Zealand observation that EPS incidence is currently decreasing over time, though the exact reason for this still remains speculative. Using a multidisciplinary approach, including the use of biocompatible solutions from the initiation of dialysis, the concomitant use of icodextrin, and/or the PD and hemodialysis combination therapy that is increasingly advocated in long-term PD, Japanese authors recently found an overall EPS incidence rate of 1.0%: it was 0.3% for PD

less than 3 years, 0.6% for PD up to 5 years, 2.3% for PD up to 8 years, and 1.2% for PD more than >8 years. These incidences are much lower than those previously described in Japan [20]. A remarkable sixfold decrease in EPS yearly incidence from 0.85% in 2009 to 0.14% in 2014 has also been found in the Dutch PD population [21]. Similar observations have been reported in Spanish, German, and Australian studies [8]. These data will need to be confirmed in the near future.

Pathology Description

The macroscopic appearance of the peritoneum of EPS patients exhibits specific characteristics. It appears tanned, thickened, and brown, with a leathery appearance [4, 16]. In contrast, the microscopic changes are not really specific and are comparable with those described in long-term PD patients. Prolonged exposure to PD solutions, with repetitive episodes of peritonitis, causes damage to the peritoneal membrane, sometimes accompanied by inflammation [22–25]. Peritoneal damage consists of denudation of the mesothelial cell layers, submesothelial fibrosis, neo-angiogenesis, and vasculopathy. Those abnormalities are also similarly present in the peritoneum of EPS patients. Some specific abnormalities, like the presence of fibroblast-like cells in the interstitial tissue, tissue deposits of fibrin and iron, and positive immunostaining for podoplanin, a membrane glycoprotein, have been reported in EPS patients [3]. The interstitium may also contain lymphocytes, especially T-helper cells [26, 27]. In another recent analysis, a series of peritoneal biopsies from EPS and an appropriately-matched cohort of long-term PD patients with similar time on PD and no EPS were compared to describe more subtle pathological changes in the peritoneal membrane of the EPS patients [28]. Markers of vasculopathy like eNOS and VEGF were significantly enhanced in EPS patients compared to uremic and control patients. An impressive finding was the 4.7-fold increase in the thickness of the submesothelial area in the EPS patients compared with the 1.9-fold in control PD patients. Using polarized light microscopy, the authors demonstrated qualitative changes in the fibrotic submesothelial tissue composition of EPS patients, with increased collagen density compared to the uremic and control PD patients. This increased density of collagen fibers was mainly caused by the accumulation of thick collagen-1 fibers, while the contribution of thinner collagen-3 fibers was not different between the groups. This is illustrated in Fig. 1. Collagen-1 is involved in wound healing and scar formation; collagen-3 accumulates in uremia [29]. These alterations in collagen matrix within the peritoneal tissue may be reflected in some functional abnormalities, because collagen binds water [30].

Pathogenesis of EPS

The morphological changes in peritoneal tissue that can develop during the time course of PD in individual patients have been described in the above part and include the mesothelium, the blood vessels, and the interstitium. Long-term exposure to unphysiological, or bioincompatible, dialysis solutions is the most important culprit [9], irrespective of the dialysis modality [31]. The percentage of long-term patients that develop marked morphological changes is unknown, because routine peritoneal biopsies and longitudinal follow-up biopsies have never been performed in adult patients for obvious reasons. Yet it is evident that only a very limited number of long-term patients develop EPS. This is the reason that the second hit theory has been ensued [32], in which an acute event like a severe peritonitis episode in a patient with an already damaged peritoneum triggers the clinical manifestations of EPS, the so-called transition from simple sclerosis to encapsulating peritoneal sclerosis [33]. Not only acute peritonitis, but also chronic inflammation could be a trigger for the transition to EPS. This is supported by the presence of activated T-cells in the interstitium [34] and the expression of several growth factors [35].

Epithelial-to-mesenchymal transition of mesothelial cells (EMT) has been described in PD patients [36]. It is characterized by the presence of cytokeratin positive fibroblast-like cells in the

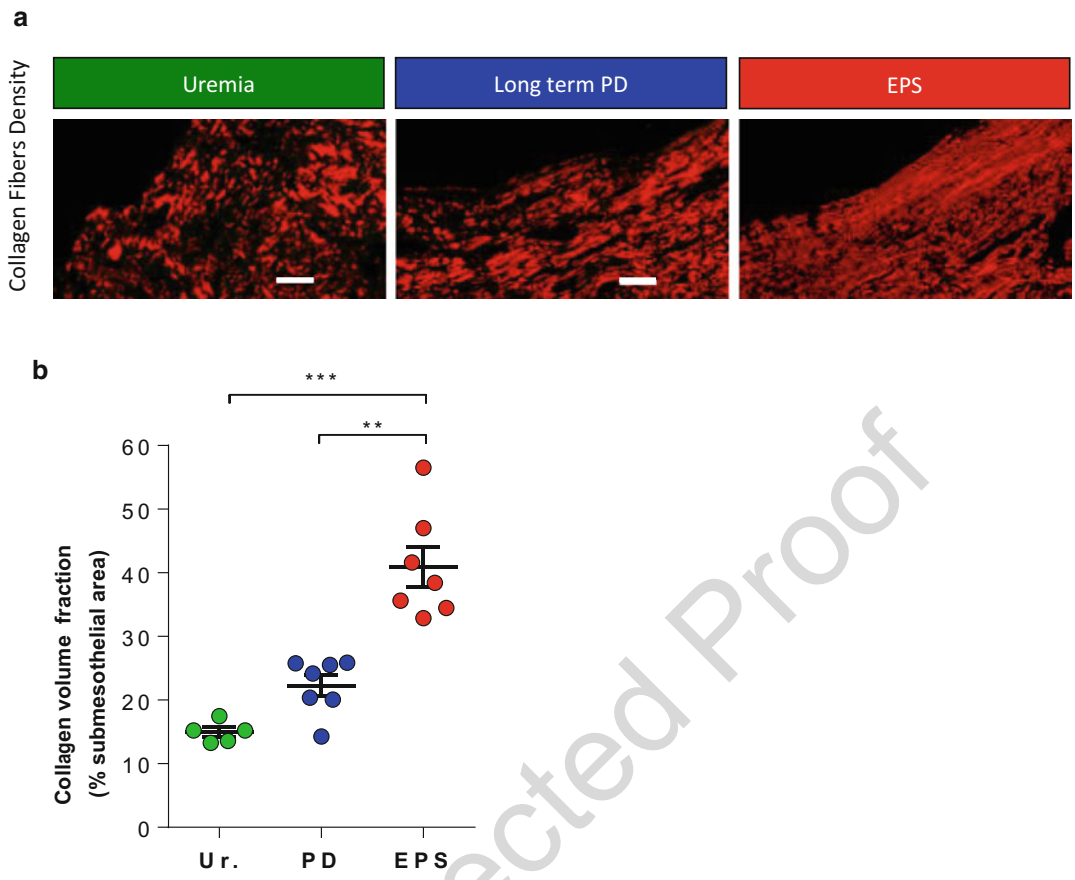

Fig. 1 (**a**) Changes in quality in the peritoneal interstitium of patients with EPS. (A-C) Representative sections of the parietal peritoneum from uremic (A), PD (B), and EPS (C) patients stained with picrosirius red and visualized under circulatory polarized light. Collagen fibers in the submesothelial area. Taken from ref. [28] with permission of the American Society of Nephrology. (**b**) Collagen volume fraction from picrosirius red-stained peritoneum as percentage of submesothelial area from uremic (green circles), PD (blue), and EPS (red) patients. Taken from ref. [28] with permission of the American Society of Nephrology

submesothelial stroma. EMT is an early event that can occur in up to one third of the patients in the second year of PD [37] and is associated with high effluent concentrations of vascular endothelial growth factor (VEGF) and the mesothelial cell marker cancer antigen 125 (CA 125) [38]. It has been suggested that EMT would predict the long-term changes in the peritoneal tissues, but this has never been substantiated due to the lack of follow-up peritoneal biopsies.

The relationship between the duration of PD and EPS points to a role of the dialysis solution in its pathogenesis. The conventional dialysis solutions are not ideally biocompatible, mainly because of the extremely high glucose concentrations and the presence of glucose degradation products. The continuous contact between glucose and proteins leads to the formation of glycosylation end products (AGEs) [39], a process that is probably enhanced by the presence of glucose degradation products [40]. Indeed, AGEs have been demonstrated submesothelially and perivascular in peritoneal tissue of long-term PD patients [41]. This may explain why the use of glucose-based dialysis solutions with a low content of glucose degradation products is associated with better preservation of the peritoneum [42–44]. Although no final proof is available, it

may well be that the decreasing incidence of EPS in some parts of the world is related to the exclusive use of biocompatible dialysis solutions.

Clinical Manifestations

Bowel obstruction in a long-term PD patient is the most important sign of EPS. The obstruction can be intermittent in the initial phase. It may cause anorexia, nausea, vomiting, weight loss, constipation or diarrhea, and abdominal pain. Blood-stained peritoneal effluent has been described but is probably rare. Some patients have signs of inflammation, like fever and a general finding of fatigue [8].

Investigations

A CT scan is currently the most appropriate imaging technique when EPS is suspected [45]. It should preferably be done with a dialysate-filled peritoneal cavity and intravenous contrast, taking precautions for the prevention of contrast nephropathy in the presence of residual urine production. Peritoneal calcifications, thickening, fluid loculation, and tethering of small bowel loops can be present [46]. An example is given in Fig. 2. Using a severity scoring system, a marked difference was found between EPS and control PD patients without this complication, but no or only mild abnormalities were present before the occurrence of clinical symptoms [47]. Therefore, CT scanning cannot be used for screening. Using a case-control approach in 15 EPS patients, 6 hallmarks for EPS could be defined: peritoneal enhancement, bowel wall thickening, calcifications, adhesions of bowel loops, obstruction, and signs of fluid loculation/septation. A positive score for three out of the six items in contrast-enhanced CT had a sensitivity of 100% and a specificity of 94% for EPS, when judged by experienced radiologists [48]. A CT scan should also be made to exclude other causes of bowel obstruction.

Some EPS patients have an elevated plasma CRP [49], but this is not always the case. Investigation of peritoneal effluent is more useful. A review of the various locally produced proteins and peptides that reflect the status of the peritoneum is given in ref. [50]. Interleukin-6 (Il-6) is a pleiotropic cytokine, produced by various cell types, including T-cells, activated macrophages, fibroblasts, mesothelial cells, and vascular endothelial cells. Effluent concentrations are usually higher than plasma concentrations. Effluent IL-6 is markedly increased during the acute phase of peritonitis [51], while some augmentation is present during minor peritoneal inflammation as defined by high peritoneal solute transport rates [52, 53]. Cancer antigen 125 (CA 125) is a high-molecular-weight glycoprotein, locally produced in the peritoneal cavity by mesothelial cells. Effluent CA 125 represents mesothelial cell mass or turnover [54]. It decreases with PD duration [55]. Vascular endothelial growth factor (VEGF) is a locally secreted glycoprotein in peritoneal fluid that is related to peritoneal solute transport in cross-sectional analyses [56]. Concentrations are higher with the use of biocompatible dialysis solutions [57]. Plasminogen activator inhibitor-1 (PAI-1) is a glycoprotein produced by endothelial and smooth muscle cells [58] and extensively present in peritoneal submesothelial tissue [59]. Effluent PAI-1 is related with solute transport and increases with PD duration [60]. A retrospective analysis of 11 patients who developed EPS after a median PD duration of more than 8 years and in whom previous data on peritoneal transport and effluent biomarkers was available showed lower values of CA 125, higher values for Il-6, and no difference for VEGF compared to a control group [61]. A subsequent analysis in the same patients showed an increase of effluent PAI-1, which started 3 years before the diagnosis of EPS [62]. The discriminative ability of PAI-1 assessed at 1 year before the clinical diagnosis was high, with an area under the receiver operating characteristic curve (ROC) of 0.76. This value is greater than those for CA 125 (0.63), Il-6 (0.62), and VEGF (0.68) [63]. The ROC value of 0.76 for PAI-1 was reflected in a high sensitivity and a moderate specificity for the diagnosis of EPS within 1 year.

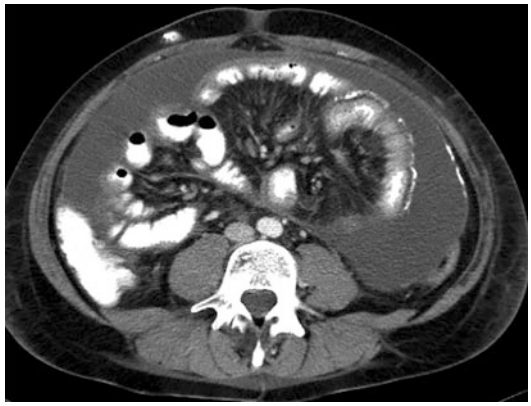

Fig. 2 A representative example of a computed tomographic scan of a patient with EPS. It shows ascites, bowel loops that are drawn into the center of the abdominal cavity indicating adhesions, and an enhanced, thickened peritoneum with calcifications both visceral and parietal. Taken from ref. [45] with permission of Oxford University Press

Poor ultrafiltration (UF) is usually present in EPS patients. This is especially the case for crystalloid osmosis-induced UF, which becomes progressively impaired [64]. Small solute transport including the absorption of glucose is fast in the majority of patients, but not progressively [17, 64–67]. Ultrafiltration failure (UFF) reflects peritoneal membrane abnormalities and should be distinguished from overhydration. Patients may become overhydrated for various reasons, UFF is one of them. Therefore, the 3x4 rule has been developed: UFF = netUF<400 mL after a 4 h dialysis dwell with a 4% (3.86/4.25) glucose-based dialysis solution. This definition was adopted by the International Society of Peritoneal Dialysis [68]. Using the above criterion in the longitudinal follow-up of 417 incident PD patients, UFF developed in 12%, but EPS in only 3% [66].

Transcapillary ultrafiltration occurs by two pathways: the small inter-endothelial pores and the intra-endothelial water channel aquaporin-1 (AQP-1). The latter has a radius of ~5 Å, which only allows transport of water without that of solutes, so-called free water transport (FWT) [69]. The magnitude of transcellular FWT is almost completely dependent on the crystalloid osmotic pressure gradient and may account for almost 50% of total ultrafiltration achieved with a 3.86/4.25% glucose-based dialysis solution in mathematical models, like the three-pore model [70]. AQP-1 also explains the sieving of sodium, the well-known phenomenon that dialysate sodium decreases with glucose-induced ultrafiltration [71]. In contrast, small pore fluid transport (SPFT) is to a large extent dependent on the hydrostatic pressure gradient. Both transport pathways, SPFT and FWT, can be assessed in individual patients by sodium kinetics [72]. Mean values for FWT during the first hour of a dialysis dwell of 35% of total UF have been reported using this technique, but with a very large interindividual variation [72, 73]. Longitudinal follow-up of 138 incident PD patients showed decreases in FWT and SPFT after 4 years of PD [74]. However, the FWT decrease was much more severe in EPS [28, 66]. Compared to time-matched controls with UFF, no other fluid transport parameter was significantly different, including net UF, osmotic conductance, ultrafiltration coefficient, and the reflection coefficient. The possibility of a reduced osmotic conductance in long-term patients with UFF has been mentioned as an explanation for the dissociation between solute and fluid transport, but the osmotic conductance was not measured [75]. The same applies for the hypothesized impaired osmotic conductance in EPS [76]. Free water transport was not assessed in these studies. All patients had a normal expression of AQP-1 [28], which suggests that filtered water, but not its soluble contents like electrolytes and glucose, is to some extent bound to constituents of the interstitium, like collagen or the interstitial matrix, that contains large quantities of hyaluronan, a very hydrophilic glycosaminoglycan [77, 78]. Whatever the cause, FWT has a very high predictive value for the clinical diagnosis of EPS in 1 year: the area under the ROC curve was 0.94, the sensitivity of FWT < 75 mL was 100%, and the sensitivity 81% in the only published study on this issue [63], as shown in Fig. 3. Addition of a dialysate PAI-1 appearance rate >8.5 ng/min increased the specificity to 94%. It should be realized that the quantitative information is from the only published study prediction of EPS and awaits confirmation by others.

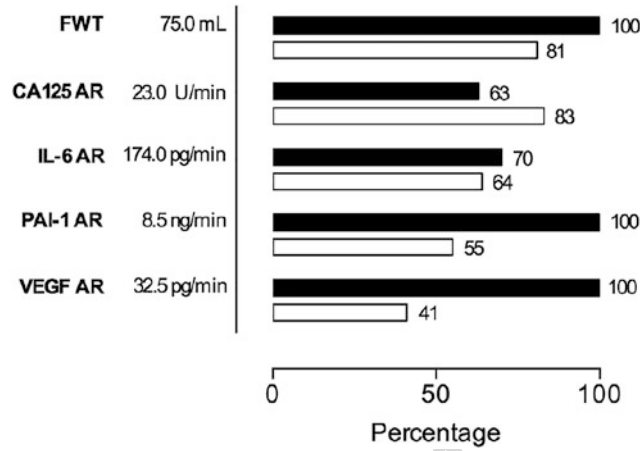

Fig. 3 Diagnostic accuracy measures are depicted for quantity of FWT_{0-60}, CA 125 appearance rate (AR), Il-6 AR, PAI-1 AR, and VEGF AR. This graph illustrates the threshold values for each parameter at a time lag of 1 year, accompanied by their corresponding estimations of sensitivity (solid bars) and specificity (open bars). Taken from ref. [63] with permission of Multimed

Treatment

It is commonly accepted that, in the presence of suspected or presumed EPS diagnosis, PD should be stopped with the transfer of the patient to hemodialysis. Unfortunately, as previously mentioned, EPS may also develop or worsen after PD withdrawal. This has led Japanese authors to advocate leaving the PD catheter in place to initiate regular peritoneal lavage after the patient had been switched to hemodialysis in order to remove pro-inflammatory cytokines, fibrin, fibrin clots, and fibrin degradation products; i.e., products suspected to mediate the peritoneal fibrotic process [79–81]. Though there are no controlled studies on this topic, such a policy has also recently been implemented in some European centers.

Because EPS is associated with high mortality rates up to 50% in the majority of series [3, 4], different interventional strategies have been proposed; they include parenteral nutritional support, specific drugs initiation, and surgery.

Reduced nutritional intake related to intestinal symptoms and persistent acute phase response lead to severe energy calorie and proteins wasting in EPS patients. Nutritional advices and monitoring are therefore mandatory, and parenteral support is often required to prevent malnutrition in patients unable to tolerate adequate oral intake or nasojejunal feeding [3, 4, 82]. In some but not all series, parenteral nutrition improved digestive symptoms, increase weight and serum albumin concentration, and decrease CRP level, but also, the general prognosis of EPS patients [17, 81, 83].

Several drug therapies have been associated with improvement in EPS condition; they include corticosteroids, tamoxifen, immunosuppressive agents, and angiotensin II blockers. Steroids, at a dosage of 0.5–1 mg/kg bw, with progressive tapering within 6 months, have been advocated because of their anti-inflammatory properties [84]. Tamoxifen, by analogy with its efficacy in retroperitoneal fibrosis, has also been tried in some patients with discordant results [85–87]. Some case reports describing the efficacy of immunosuppressive agents, like azathioprine, mycophenolate mofetil, or a switch from calcineurin inhibitors to sirolimus in post-renal transplant EPS, or angiotensin II blockers, have also been reported. However, those data are too anecdotic to strongly recommend their utilization in the management of EPS [8]. It is indeed difficult to believe that a pharmaceutical agent could revert EPS symptomatology once the bowels are completely encapsulated in a cocoon. That is the reason why early corticosteroids prescription in patients in whom a diagnosis of EPS is suspected should be strongly recommended.

Surgery, initially contra-indicated because of its related morbidity and mortality rates, is now widely recommended in selected cases, i.e., EPS patients in whom nutritional status has been corrected and corticosteroids dosage tapered to a minimal dose. Successful surgical results had repeatedly been reported from Japanese centers.

The surgery consists of an enterolysis, i.e., a decortication of the fibrous peritoneal membranes, relief of localized intestinal stenosis with balloon dilatation after enterolysis, and prevention of re-obstruction recurrence by localized intestine suture (the Noble plication procedure), while avoiding inadvertent bowel perforation. By-pass between the jejunum and large intestine or ileum is often required [86–88]. Post-operative mortality may reach up to 6%. Similar techniques have also been initiated in the UK and Germany in specialized surgical teams [89–91]. Mortality rates in the long term are reduced in operated patients from ~50% in patients without surgery to ~30 after an operation, but high morbidity and relapse rates have been reported. [92, 93]

Prevention

Currently no definitive criteria exist that enable detection of early stage of EPS. But, as EPS incidence increases with time on PD, markedly after 4–5 years of treatment, the question has been raised if PD should be discontinued pre-emptively in patients after some years, especially in those awaiting transplantation [85, 94]. This view was strongly opposed by many well-known nephrologists [95, 96], especially because a majority of PD patients will not develop EPS and EPS may become manifest after discontinuation of PD. Recently published results from the ANZDATA and Scottish registry are also supportive for not setting an expiry date, because the estimated risk of developing EPS with the duration of PD appears to be country-specific and much smaller when the competing risk of death was taken into account, instead of the Kaplan–Meier approach [97].

No predictive models are currently available to predict the risk of EPS from baseline. A better understanding of the early stages of EPS would therefore help to identify patients at risk and establish prevention strategies. Who are the patients at-risk to develop EPS? Probably those who develop a fast solute transport status with impaired ultrafiltration, although the percentage of them is very small. But it justifies yearly assessment of peritoneal function using a modified peritoneal equilibration test (PET), performed with a 3.86/4.25% glucose-based dialysis solution and a dialysate and blood sample after 1 h [68]. The test provides information on D/P creatinine, net UF, and sodium sieving. When this PET is augmented with temporary drainage after 1 h for volume assessment by weight, followed by reinfusion, FWT can also be calculated [98]. Although based on a limited number of patients, FWT had a very high area under the receiver operating characteristic curve for the clinical diagnosis of EPS within 3 years [63].

Other strategies for EPS prevention have been recommended; they include, first, glucose-load minimization by the use of loop diuretics if appropriate, and alternative osmotic agents to glucose, such as amino acids and icodextrin, and second, prescription of the so-called more biocompatible-physiological new glucose-based dialysate solutions [1, 4, 8, 18, 21]. Two cross-sectional morphological analyses have been published in adult patients comparing dialysis with a conventional solution with a biocompatible one [42, 44]. Both reported less vasculopathy and fibrosis in those treated with the biocompatible solution. In contrast, peritoneal abnormalities were present in children on biocompatible solutions, but the source of the solution was not reported and may have been different [100]. The global fluid study focused on differences in the time course of D/P creatinine reported stable values on the biocompatible solution, in contrast with the rise in those treated with conventional solutions [100]. FWT in patients treated with the biocompatible solution showed a small, not significant decline during follow-up [101]. It is speculative if the decreasing incidence of EPS reported in some countries can be explained by the larger number of patients treated with biocompatible dialysis fluids [1, 8, 20, 21]. According to our current knowledge of the pathogenesis of EPS, the best prevention is probably the replacement of conventional dialysis solutions by the biocompatible ones, including icodextrin. Yearly monitoring of peritoneal function including ultrafiltration and free water transport when

possible should identify patients at risk for EPS development.

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