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REVIEW

Management of encapsulating peritoneal sclerosis: a guideline on optimal and uniform treatment

S.M. Habib[1], M.G.H. Betjes[1*], M.W.J.A. Fieren[1], E.W. Boeschoten[3], A.C. Abrahams[4], W.H. Boer[4], D.G. Struijk[5], W. Ruger[6], C. Krikke[7], R. Westerhuis[8], R.G.L. de Sévaux[9], F.M. van der Sande[10], A. Gaasbeek[11], M.R. Korte[2] - on behalf of the EPS registry

[1]Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands, [2]Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, the Netherlands, [3]Hans Mak Institute, Naarden, the Netherlands, [4]Department of Internal Medicine, University Medical Centre, Utrecht, the Netherlands, [5]Department of Internal Medicine, Academic Medical Centre, Amsterdam, the Netherlands, [6]Department of Internal Medicine, VU University Medical Centre, Amsterdam, the Netherlands, Departments of [7]Surgery, [8]Internal Medicine, University Medical Centre, Groningen, the Netherlands, [9]Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, the Netherlands, [10]Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands, [11]Department of Internal Medicine, Leiden University Medical Centre, Leiden, the Netherlands, *corresponding author: tel.: +31 (0)10-7040704, fax: +31 (0)10-7035756, e-mail: m.g.h.betjes@erasmusmc.nl

ABSTRACT

Encapsulating peritoneal sclerosis (EPS) represents a rare complication of long-term peritoneal dialysis (PD). It is characterised by diffuse peritoneal membrane fibrosis, progressive intestinal encapsulation and the clinical spectrum of intestinal obstruction. The pathogenesis is as yet not well understood but includes inflammation, angiogenesis and fibrosis. The current diagnosis of EPS lacks specificity and relies on clinical, radiographic or macroscopic evaluation. There is no general agreement on managing EPS although accumulating clinical data suggest drug treatment (steroids, tamoxifen), surgery (enterolysis) or a combination of both. Here, we provide a short overview on the current knowledge of EPS, with a focus on treatment. Moreover, we present a diagnostic and a therapeutic algorithm for EPS based on the best available published data and our combined experience.

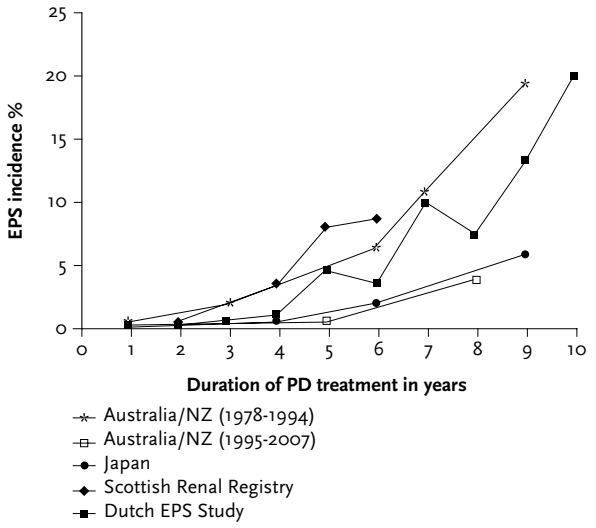
KEYWORDS

Encapsulating peritoneal sclerosis, enterolysis, immune suppressive, management algorithm, peritoneal dialysis

INTRODUCTION

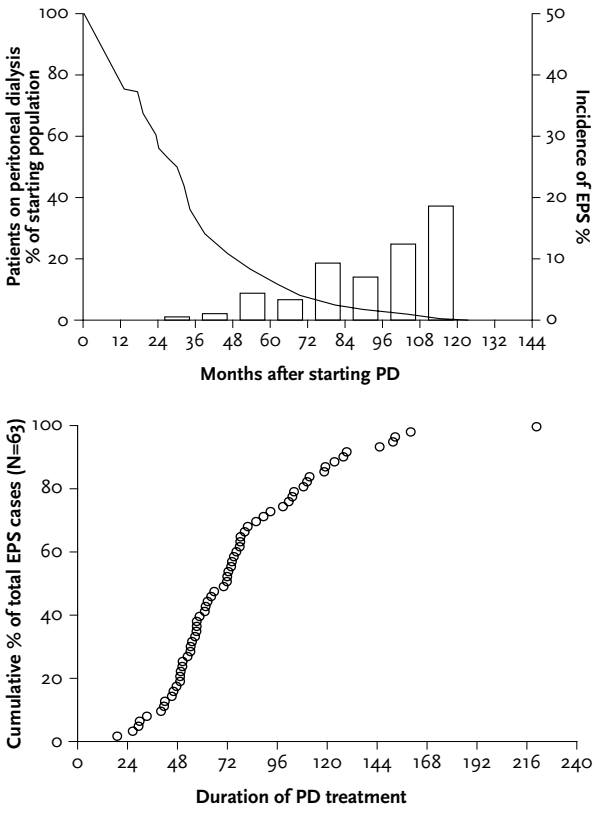
Encapsulating peritoneal sclerosis (EPS) complicating peritoneal dialysis (PD) is a rare disease of the peritoneum characterised by the presence of an inflammatory and fibrotic peritoneal capsule, which partially or completely entraps the bowel.[1] The reported prevalence of EPS within the PD patient population ranges worldwide from 0.7 to 3.7%.[2-5] The time on PD is the most important risk factor for EPS, possibly because it represents the time the peritoneum is exposed to the potential harmful effects of dialysis fluids.[4] Other possible factors associated with the development of EPS include age at the start PD, number of peritonitis episodes, fast peritoneal membrane transporter status, loss of ultrafiltration, and kidney transplantation.[6,7] Within the first few years of PD treatment, the incidence of EPS is usually less than 1%, but rises significantly after two to three years exceeding 15% in the group of patients on PD for ten years or more (*figure 1*). The overall number of patients on PD rapidly decreases within the first years after starting PD and after three years only 25% of the original cohort were treated with PD (*figure 2*). Still, over 90% of all EPS cases are treated with PD for more than three years (*figure 2*). Unfortunately, the early stages of EPS are difficult to recognise although progressive loss of

Figure 1. *The incidence of encapsulating peritoneal sclerosis (EPS) in relation to duration of peritoneal dialysis (PD) treatment. The EPS incidence is not cumulatively shown and should be interpreted as the percentage of patients diagnosed with EPS within the population of patients treated with PD for a given number of years (shown on the x-axis)*



Data from Australia/New Zealand for two time periods (Rigby, 1998 and Johnson, 2010),[2,5] Japan (Kawanishi, 2004),[3] Scotland (Brown, 2009),[32] the Netherlands (Korte, 2011)[7] are shown.

Figure 2. *The top figure shows the percentage of patients who remain on peritoneal dialysis (PD) after starting treatment (black line, total number patients 126). The bars show the incidence of encapsulating peritoneal sclerosis (EPS) as the percentage of patients diagnosed with EPS within the population of patients treated with PD for a given number of months (shown on the x-axis). The bottom figure shows the cumulative percentage of EPS patients in relation to their time of treatment with PD*



All data were obtained from the Dutch EPS study (Korte, 2011)[7].

ultrafiltration is frequently observed in patients who go on to develop EPS.[8,9] The consequences of EPS are devastating and mortality rates exceed 50%, most commonly because of complications related to persistent bowel obstruction (e.g. perforation) and prolonged parenteral feeding.[2,5,10] Most cases of EPS (>50%) are reported after PD treatment has been stopped either because of symptoms of EPS, a non-resolving peritonitis, or kidney transplantation.[3,7] The last-mentioned condition is coined post-transplantation EPS and has been described as a novel entity.[11,12] Post-transplantation EPS has a major negative impact on patient survival after kidney transplantation and EPS-related mortality is the fourth known cause of death in this patient population.[13]

Timely diagnosis and treatment of EPS seems warranted as it may offer the opportunity for resolving the bowel obstruction at an early stage, before complete encapsulation has occurred. Unfortunately, there is much uncertainty and delay in establishing the diagnosis of EPS. Furthermore, there is a lack of consensus on best therapeutic options to guide the management of EPS.

The Dutch EPS registry was successfully launched in June 2009 and is currently collecting clinical data as well as related biological patient material of cases with a possible or definite diagnosis of EPS. It is a collaboration of the Dutch kidney centres and the Hans Mak Institute.[14] Also an expanding international collaboration with the UK registry and other European countries has been established recently.[15] The main goal of the registry is to track the routine clinical outcomes of patients with EPS and contribute to a better medical understanding of the disease. The present article provides a short overview of the current knowledge on EPS, with a focus on treatment. We outline a rational strategy that can be used to guide the diagnosis and treatment of patients with EPS.

PATHOGENESIS

Appreciating the current knowledge on the mechanisms that lead to EPS is essential for the development of a management approach.

EPS can be considered an inflammatory repairing response of the peritoneum that has been damaged by chronic exposure to bio-incompatible dialysis fluids.[16,17] In an attempt to create a comprehensive overview of the disease, Kawanishi classified the disease into different stages.[18] In the early stages of EPS, the thin encapsulating membrane shows active inflammation. This is followed by elaboration of a thickened fibrotic membrane that progressively impairs normal bowel movement. Eventually, the inflammation subsides and a thick acellular fibrotic membrane remains that encloses the intestines.[19] During PD treatment the peritoneal changes include submesothelial thickening and fibrosis, accompanied with neoangiogenesis.[20] A key pathological mechanism may be the epithelial to mesenchymal transition (EMT) of mesothelial cells (MC). In this process, new fibroblast cells arise from local conversion of MC by EMT.[21,22] Although it is as yet unclear to what extent EMT is also present in EPS development, TGF-beta is one of the central regulators.[23] Other growth factors and molecules may also play a role in the development of EPS. In an experimental model of EPS, it was for instance noted that vascular endothelial growth factor is important in the EPS-like changes of the peritoneal membrane.[24]

EPS usually develops after long-term PD, but not all long-term PD patients will necessarily develop EPS. Which factors cause or allow its development is not exactly known but a second hit may be an important trigger. The 'two-hit theory' hypothesises that the preconditioned thickened and transformed peritoneum undergoes a second hit triggering symptomatic EPS.[25] This second event may be peritonitis, transplantation, or discontinuation of PD.[1,26]

DIAGNOSIS

The diagnosis of EPS lacks specificity but should include the clinical spectrum of intestinal obstruction with or without the existence of inflammation parameters and the presence of peritoneal sclerosis confirmed by macroscopic inspection or radiological findings.[27] The appearance of ultrafiltration failure, bloody ascites and elevated markers of inflammation such as C-reactive protein (CRP) may express the early inflammatory nature of the disease.[18] Unfortunately, in most cases EPS is diagnosed when abdominal pain due to recurrent or chronic bowel obstruction becomes clinical manifest.[28,29] Physical examination may indicate the presence of ascites or ileus in the abdomen. In some instances a palpable abdominal mass is found.[30] As none of these findings are specific, other diagnoses such as infections, tuberculosis, pancreatitis and malignancies (e.g. lymphoma) should be ruled out.

The provisional diagnosis of EPS is usually made after radiographic evaluation by CT scan showing a characteristic picture of a thickened peritoneum encapsulating the intestines.[31-33]

In case of clinical suspicion and a negative CT scan, diagnostic surgery (laparoscopy or laparotomy) can provide the diagnosis.[25,34] It also facilitates taking peritoneal biopsies to detect early EPS or exclude other causes.[35] However, surgical exploration is a challenging decision as extensive peritoneal fibrosis and bowel loops adherent to each other may exist.[1] Therefore, we advocate performing timely diagnostic surgery to establish the diagnosis of EPS with certainty.

TREATMENT

Cessation of PD treatment

An important initial step in the management of EPS is cessation of PD to prevent further peritoneal damage.[27,36,37] Although this approach seems reasonable, it is a matter of debate as this approach does not always reverse the progression of peritoneal fibrosis.[38] A logical explanation might be the absence of peritoneal lavage to remove fibrin, profibrotic factors and cytokines. Studies show that more than half of EPS cases are often diagnosed two years after stopping peritoneal dialysis and less severe cases of EPS may even worsen after discontinuation of PD.[3,32,39] Leaving the catheter in situ and performing regular peritoneal lavage in patients who have discontinued PD has been tried in Japan. However, no convincing evidence of a beneficial effect on the course of EPS has been reported yet.[3,40,41]

A clear statement on withdrawing patients from PD after the diagnosis of EPS has been established may be difficult. But given the association between PD duration and progression of EPS we propose a switch from PD to haemodialysis with removal of the PD catheter.

Immune suppressive medication

There is no agreement on the use of immune suppressive drugs to treat EPS. This is largely due to a lack of targeted pharmacological therapies and absence of trials with a significant number of patients. Immunosuppressants such as azathioprine, myocophenolate mofetil and sirolimus have been used in patients with EPS, usually co-administered with corticosteroids.[42-44] But the available data are limited to anecdotal reports and the superiority of these drugs to corticosteroids alone is not proven. Here we summarise the two best-documented management strategies for EPS, corticosteroids and tamoxifen. We propose an algorithm which is based on a critical appraisal of published data and our combined experience.

Corticosteroids

Corticosteroids are the most reported and successfully used drugs in treating EPS. Steroids are thought to

be effective in suppressing the inflammatory process of the peritoneal membrane and inhibiting collagen synthesis and maturation.[45] Thickening of the peritoneal membrane may even disappear. In Japan, the use of corticosteroids as first-line therapy has gained widespread acceptance. In a report by Kuriyama *et al.* all patients treated with corticosteroids maintained good prognosis after the diagnosis of EPS. Patients who did not receive corticosteroid therapy died within eight months of diagnosis.[46] Similarly, others have reported lifesaving treatment with corticosteroid therapy.[40,44,47-49] Only one series has reported a clinical improvement rate of 38.5% in patients treated with corticosteroids alone.[3]

Importantly, the use of immune suppressive medication only seems appropriate in case of ongoing inflammation. Albeit aspecific, this can only be assessed by clinical observation of the patient's status and laboratory measurements of levels of inflammatory biomarkers, such as CRP.[18,48,50] In the late stages of EPS, surgery may be more effective as the inflammatory tissue seems to be gradually replaced by fibrosis and is less likely to shrink with medical therapy.[18] However, there are no data to support this view and in our experience almost all patients are inflammatory to some degree.

Although the optimum dose and duration of steroid therapy have not been established by a controlled trial, most publications support a regimen of prednisolone 0.5 to 1.0 mg/kg/day or a pulse dose of 500 to 1000 mg methylprednisolone for two to three days.[3,25,46,47,51,52] The dose of prednisolone needs to be approximately 0.5 to 1.0 mg/kg/day during the first month, 0.25 to 0.5 mg at months 2 and 3 and thereafter tapered to 10 mg at six months. Treatment with steroids must be continued for at least one year. It is important to prolong the period of high-dose steroids in a responding patient with a persistently elevated CRP level as dose reduction may result in recurrence of intestinal obstruction and inflammation, responding to retreatment with prednisolone.[48] Of course, the well-known potential adverse effects of prednisolone should be taken into account but the high mortality of EPS tips the balance in most cases in favour of treatment. Peritonitis, particularly caused by tuberculosis, should be ruled out as far as possible.[53] Any sudden rise in CRP level not adequately responding to steroids should raise the suspicion of a bacterial peritonitis because of spontaneous small bowel perforation.

Tamoxifen

Tamoxifen is a selective oestrogen receptor modulator (SERM), which has been successfully used in fibrosclerotic disorders such as fibrosing mediastinitis, sclerosing cervicitis, desmoid tumours, retroperitoneal fibrosis, and Dupuytren's contracture.[54-57] In recent years, the use of tamoxifen in the treatment EPS patients has gained more interest. Allaria *et al.* were the first to describe the successful use of tamoxifen in an EPS patient.[58] The therapeutic potential of tamoxifen therapy is also confirmed in a significant proportion of other reported cases. Most reports show improvement of the intestinal function and a decrease in inflammation and fibrosis.[59-61]

The largest controlled series by the Dutch EPS study showed a decreased mortality in a group of EPS patients treated with tamoxifen (45.8 *vs* 74.4%, p=0.03) compared with a group who were not.[62] Remarkably, a large case series from the UK showed no improvement in survival rate when tamoxifen was used.[63] This discrepancy in survival outcomes may be the result of including more severe cases in the Dutch study.

Although the specific working mechanism of tamoxifen remains to be defined, it appears different from the treatment of breast cancer. In the latter, its main action is through binding of active metabolites to the oestrogen receptor (ER).[64] Inhibition and modulation of TGF-beta, which are ER-independent pathways might be the rationale behind the positive results in fibrotic diseases.[65] Interestingly this was underlined by findings from a recent study by Braun *et al.* showing almost no ER expression in the peritoneal tissue of EPS patients.[66]

Tamoxifen is an alternative to the (long-term) use of corticosteroids as its side effects are mild compared with prednisolone. When remission on corticosteroids is absent additional tamoxifen can be considered. Alternatively, when there is doubt of an underlying inflammatory EPS, tamoxifen may be considered to be first choice. Unfortunately no data exist to support this view as there are no comparative studies for tamoxifen and corticosteroids, and tamoxifen is nearly always given in combination with steroids. In the Dutch EPS study, the multivariate analysis with adjustment for concomitant prednisone use in the tamoxifen-treated group confirmed the trend of improved survival.

Most studies in EPS report a tamoxifen dose between 20 and 40 mg/day.[59,60,67-70] This is similar to that used in retroperitoneal fibrosis.[56,71] After the introduction of tamoxifen therapy, favourable clinical outcomes are often seen within two to six months.[51,58,67,69] When there is clinical improvement the treatment with tamoxifen is probably maintained for a longer period analogous to recommendations on retroperitoneal fibrosis.[56] We recommend an initial dose of 20 mg twice daily for at least one year. The CT scan can be used to monitor resolution of peritoneal thickening and fluid collection after tamoxifen therapy.[59] Tamoxifen may have beneficial effects in the management of EPS but caution is warranted and more studies are needed to confirm its (adverse) effects. In addition, the adverse effects of tamoxifen such as strokes, thromboembolic events, hot flushes, and endometrial carcinoma have to be considered carefully

for each patient.[72,73] Reported adverse effects of tamoxifen in the EPS literature include arteriovenous access thrombosis, pulmonary embolism, thrombopenia, and calciphylaxis.[59,52,60]

Surgery

Surgical treatment has created exciting possibilities in the management of EPS. New surgical techniques have gained broad attention and nowadays even specialised referral centres for surgery have been established in the UK.[74]

In the past, mortality rate as a result of surgical complications was high and prognosis post-surgery was poor.[75,76] The new surgical technique of enterolysis has shown to be successful in treating more than 92% out of 130 EPS patients with a postsurgical mortality of 6.9%.[77] The procedure of enterolysis implies the ablation of fibrotic tissue and lysis of the adhesions.[25] Of note, a peritonectomy as part of the surgical approach in EPS has been used in Manchester, but no large-scale studies have been published yet.[74]

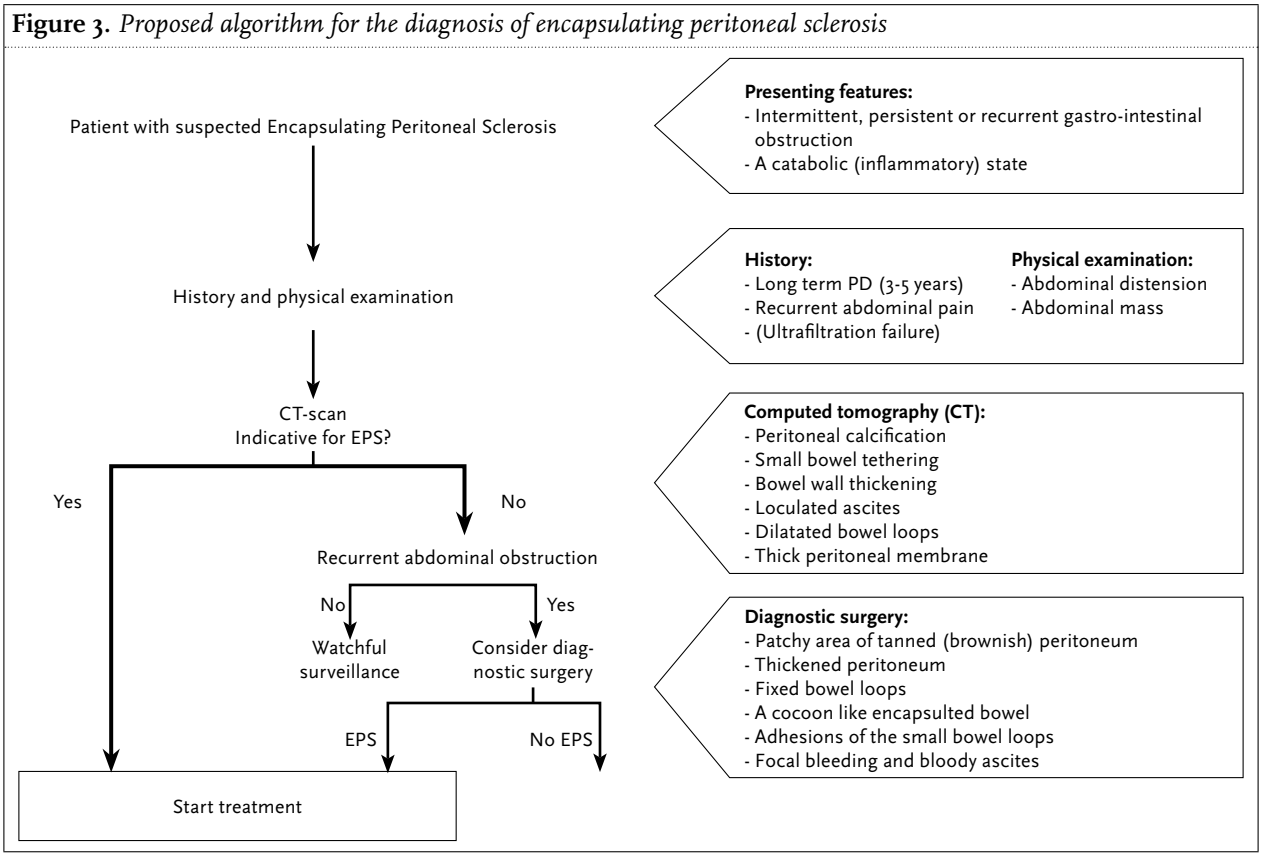
The surgical procedure to remove the adhesive lesion may be extremely time consuming, demanding and very hazardous. It is proposed that surgery should be performed if the patient does not get better with conservative or medical therapies.[78] Surgery is indicated after the inflammation has subsided and if ileus symptoms become pervasive.[18] Sometimes the encapsulation is very localised and in these cases, it tends to be at the ileocecal part of the intestines.[79,80] These EPS patients benefit most from a relatively easy to perform localised peritonectomy.

Some complications after surgical intervention include recurrent intestinal obstruction, formation of fistulas, or sepsis due to a perforated intestinal wall.[30] In addition, surgery may not always exclude the recurrence of adhesions or symptoms of bowel obstruction. In a report by Kawanishi *et al.* 33 (25%) of the 130 patients required re-surgery.[81] In order to prevent re-obstruction, suturing intestine to intestine as part of the Noble procedure has been described and also postoperative prophylaxis with steroids or tamoxifen might be useful.[77]

Nutritional management: total parenteral nutrition

The decision on planning patients for nutritional support is necessary to prevent malnutrition as this is a major problem in EPS.[39] A study from the UK has highlighted the importance of total parenteral nutrition (TPN) and dietary counselling in the integral approach of EPS. In a group of EPS patients undergoing surgery, improved surgical outcomes were reported when TPN was used as part of the preoperative care.[82] The authors recommend careful monitoring of the nutritional status by use of markers such as albumin. With regard to this statement, we would like to

Figure 3. *Proposed algorithm for the diagnosis of encapsulating peritoneal sclerosis*



underline the negative correlation between inflammation and markers such as albumin.[83]

However, TPN is not a curative therapy as low recovery rates are observed when it is used alone.[3,78] The Pan Thames study also observed shorter time to death (10 months, range 0 to 101) in the TPN treatment group compared with patients maintained on oral nutrition (15 months, range 0 to 119).[63] Although there was no information on the initial nutritional status or clinical condition of patients the difference in survival could be due to TPN-related complications such as infections.[84]

CONCLUDING REMARKS

EPS is an infrequent but severe complication of PD with the incidence increasing progressively with the duration of dialysis. A high degree of suspicion for EPS in any (former) PD patient with signs of bowel obstruction is warranted. Given the current published data and our experience with EPS cases, there is a rationale for corticosteroids, tamoxifen and surgery in the treatment of EPS. Integrating the available data, we have developed algorithms for the diagnosis and treatment of EPS (*figure 3* and *4*).

A multidisciplinary approach to the patient with EPS is needed and should at least involve a nephrologist, dietician and surgeon. In addition, a specialised surgical centre or surgeon is needed in the Netherlands to ensure a high standard of quality for this challenging and time-consuming abdominal surgery in EPS patients. Studies on the complex pathogenesis and the role of inflammatory-mediated mechanisms are needed and may provide new clues for treatment. Finally, the optimum dose and duration of steroid therapy and the benefits of tamoxifen need to be further investigated.

We encourage physicians to submit every suspected or proven case of EPS to the Dutch EPS registry at www.epsregistry.eu.

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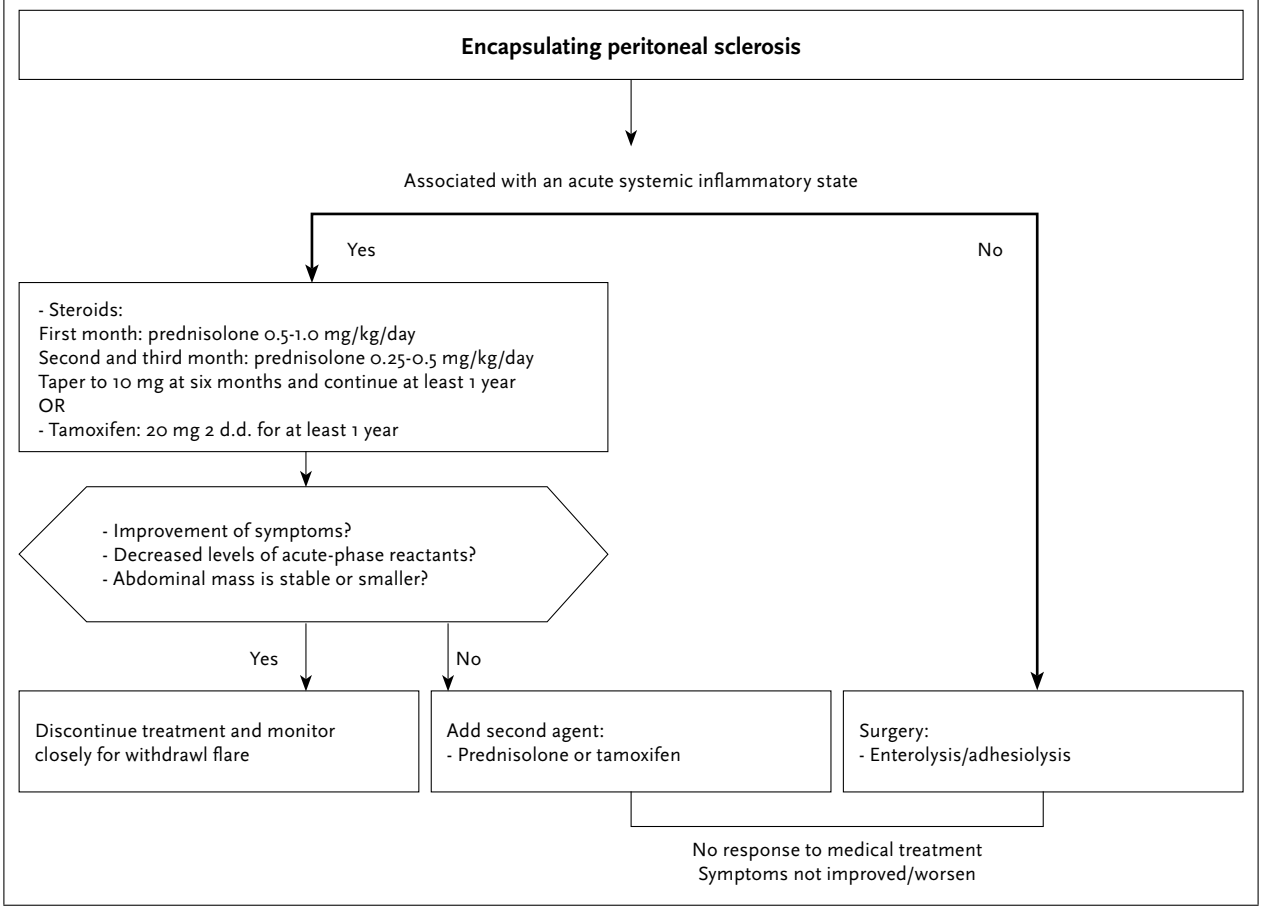
Figure 4. *Proposed algorithm for the treatment of encapsulating peritoneal sclerosis*



the EPS registry include: E. Steyerberg and H. Lingsma, Epidemiology, Erasmus MC, Rotterdam. The EPS Registry is supported by the Hans Mak Institute.

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