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## Abdominal cocoon: An enigmatic entity

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### ABSTRACT

Abdominal cocoon, variously described as encapsulating peritoneal sclerosis (EPS) or sclerosing encapsulating peritonitis or peritonitis chronica fibrosa incapsulata, represents a syndrome of clinical symptoms related to formation of a fibro-collagenous peritoneal membrane that involves the small intestinal loops. It is the outcome of several different etiologic processes. The major factors associated with development of an abdominal cocoon include continuous ambulatory peritoneal dialysis, tuberculosis, post-renal or liver transplant, use of beta-blockers although a proportion are of idiopathic origin. It is believed that the pathogenesis is driven by epithelial-to-mesenchymal transition of the mesothelial cells. The clinical presentation is related to development of altered gut motility resulting in abdominal pain and features of intestinal obstruction. Surgery is usually required in cases of unremitting intestinal obstruction. Although computed tomography may provide a pre-operative diagnosis, many cases are diagnosed at the time of surgery. Role of conservative therapy using drugs like steroids, tamoxifen, and mechanistic target of rapamycin (mTOR) inhibitors, or antitubercular therapy (in patients with tuberculosis) is uncertain. Early management aimed at the underlying etiological factor may ameliorate the symptoms and halt progression to formation of frank cocoon. Occasionally, conditions like peritoneal carcinomatosis or peritoneal encapsulation may mimic EPS.

**KEYWORDS:** Encapsulating peritoneal sclerosis; tuberculosis; peritoneal dialysis; betablockers; adhesiolysis; intestinal obstruction.

### Introduction

Abdominal cocoon or “Encapsulating peritoneal sclerosis” (EPS) was previously termed as sclerosing encapsulating peritonitis (SEP) and is an uncommon cause of intestinal obstruction. It was first described in 1907 by the term

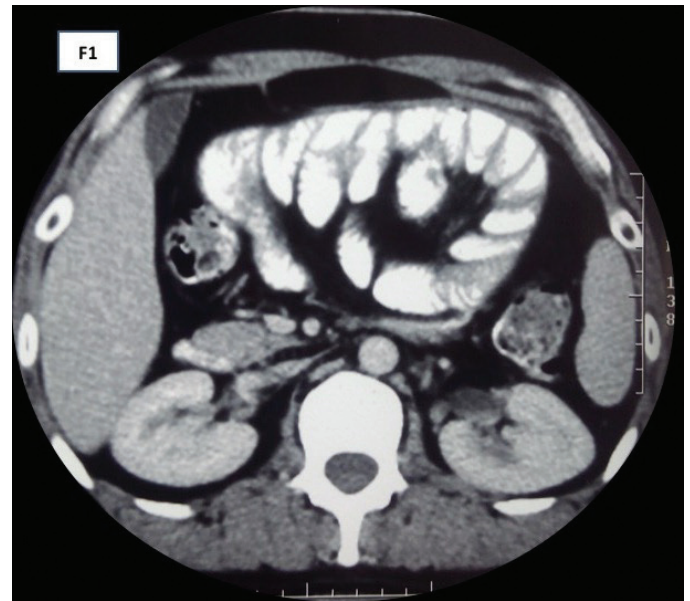
“peritonitis chronica fibrosa incapsulata” and later in 1978 after its detailed description as “abdominal cocoon”.<sup>1</sup> It is believed to be a result of a chronic intra-abdominal fibro-inflammatory process that results in formation of fibrous

tissue sheets that cover, fix and ultimately constrict the gut compromising its motility. This eventually leads to a marbled, thickened, leathery fibro-connective tissue sheath like structure that envelopes the small intestine in the form of a cocoon (**Figure 1**). Various terminologies have been used however EPS seems the most appropriate as it is self-descriptive with encapsulation of intestine resembling a cocoon and damage to the peritoneal membrane (peritoneal sclerosis). In advanced cases, inflammatory features are not always apparent, so the use of word peritonitis as in SEP is not preferred.<sup>2</sup> Indeed this name has been proposed as the appropriate term by the international society for peritoneal dialysis (ISPD) when cocoon formation or related changes occur in setting of the peritoneal dialysis.<sup>3</sup> However, it may be prudent to use this term in all clinical situations as the process seems to be the same result of different predisposing factors. Due to its nonspecific presentation during initial stages, before cocooning has fully developed, and non-availability of markers for early identification one needs to have a high index of suspicion in a given clinical scenario to reach a diagnosis. The present review will discuss the etiology, pathogenesis, pathology, clinical presentation, diagnostic evaluation, and treatment strategies with summary through management algorithm and concludes with the preventive strategies for this enigmatic condition.

## Etiology

In its first description by Foo et al in 1978 in adolescent girls from tropical and sub-tropical areas it was called primary or idiopathic EPS as the etiology was obscure.<sup>1</sup> This was proposed to be retrograde peritonitis from spread of infection through fallopian tubes and retrograde menstruation with subsequent immunologic damage. However, later as it was also described abundantly in men, premenopausal females and children there seem little credence to this hypothesis.<sup>4-6</sup> A possibility of developmental abnormality cannot be ruled out, as abdominal cocoon has been associated with omental hypoplasia and mesenteric vascular malformation.<sup>7</sup>

Apart from the primary variant, EPS is classified as secondary when there are identifiable underlying



**Figure 1:** CT image of abdominal cocoon showing cauliflower sign.

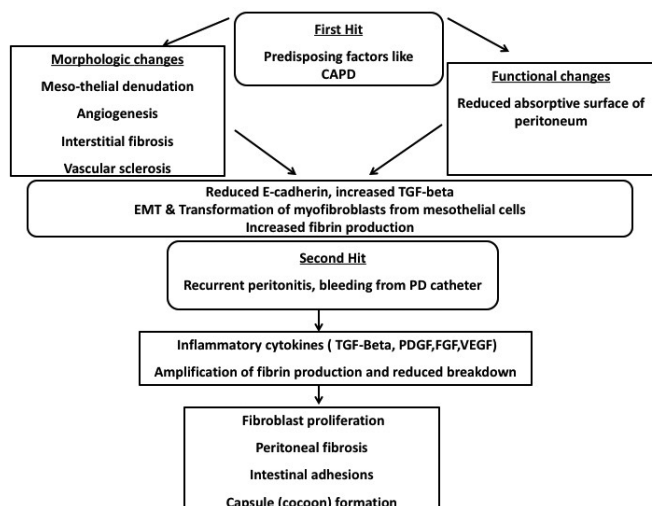
triggering factors that may include continuous ambulatory peritoneal dialysis (CAPD) with recurrent peritonitis which can be due to bacterial infection or sterile chemical peritonitis, peritoneal tuberculosis, use of certain drugs like beta blockers especially the historical drug practolol, methotrexate, asbestos, use of intraperitoneal chemotherapy, LeVeen shunt, ventriculoperitoneal shunts, systemic lupus erythematosus, sarcoidosis, luteinized thecoma of ovary, ruptured dermoid cyst among others.<sup>8</sup> Besides these there have been reports of various rare and uncommon etiologies for cocoon summarized in **Table 1**.<sup>9-18</sup>

A close differential for EPS is peritoneal encapsulation. It's a congenital abnormality where in the small bowel is enclosed in a sac of accessory peritoneum derived from yolk sac due to abnormal return of the physiological umbilical hernia in the abdominal cavity during the twelfth week of gestation. It can involve part or whole of the small intestine. It's usually an incidental finding during laparotomy for some other indication and rarely can present with intestinal obstruction, gangrene or aortic occlusion. If encountered in symptomatic patients it needs to be excised with lysis of inter-loop adhesions if present.<sup>19,20</sup>

### Pathogenesis

The peritoneal stromal and mesothelial reaction to the various etiologic factors for EPS results in inflammation giving way to peritoneal sclerosis or fibrosis that finally leads to cocoon formation. Chronic irritation of the peritoneum whether chemical or infective, disrupts the mesothelial cell junction damaging the subserosal tissue setting an inflammatory response ending in fibrosis.<sup>21</sup> In an experiment, household bleach was used in rats to start chemical peritonitis and later blood was instilled, the initial event caused membrane damage and the later lead to clot formation bringing the visceral surfaces together. This demonstrated that two events brought fibrosis, coagulation and inflammation together leading to cocoon formation.<sup>22</sup> Analogously recently the pathogenesis of EPS has been explained by the “Two Hit hypothesis” that states that two factors are required for onset of EPS.<sup>2</sup> Pathogenic mechanisms which contribute to genesis of EPS are shown in **Figure 2**.<sup>21,23,24</sup>

A predisposing factor that causes functional and morphological damage to the peritoneum like in peritoneal dialysis, chronic exposure to the dialysate results in mesothelial disruption (first hit) setting the ground for further development of sclerosis. An initiating factor in the form of an inflammatory stimuli superimposed on the damaged peritoneum like in recurrent peritonitis



**Figure 2: Chart depicting pathogenic mechanism (Two hit hypothesis) in abdominal cocoon.**

**Table 1: Causes of abdominal cocoon**

Common
• Idiopathic
• Peritoneal Dialysis related
• Tuberculosis
• Malignancy (Neuroendocrine tumours, Thecomas, Ruptured tumours like GIST or dermoids)
• Post-operative (Renal transplantation, Liver transplant, laparotomy, use of Povidine iodine)
• Drugs (Beta-blockers, Ergot)
• Generalized peritonitis (bacterial, eosinophilic, meconium)
Uncommon
• Cirrhosis
• Endometriosis
• Hyper-thermic peritoneal perfusion
• Familial Mediterranean fever
• Hemodialysis
• Systemic lupus erythematosus
• Abdominal trauma
• Mycobacterium bovis
• HIV
• Whipple’s disease
• Peritoneo-venous and ventriculo-peritoneal shunts
• Protein S Deficiency
Associations
• Cryptorchidism
• Omental hypoplasia
• Peritoneal encapsulation
• Mal-rotation
• Treitz’s hernia

(second hit) in the setting of PD. The characteristics of the dialysate like acidity, high glucose and advanced glycation end products, hyper-osmolarity etc cause the first hit by causing mesothelial denudation and subsequent upregulation of profibrotic growth factors like TGF-beta, platelet derived growth factor (PDGF), tumour necrosis factor (TNF)-alpha setting the stage for fibrosis.<sup>24</sup> Also under the influence of transforming growth factor (TGF)-beta, mesothelial cells express plasminogen activator inhibitors (PAI) 1 and 2 leading to decrease in fibrin

degradation.<sup>24</sup> Also, exposure to drugs like practolol has been shown to cause mesothelial cell disruption (first hit) that leads to the cascade of events leading to EPS.<sup>23</sup> The damage to mesothelium causes down-regulation of E-cadherin with loss of cell to cell contact and apical basal polarity and with the upregulation of TGF-beta there is epithelial to mesenchymal transformation with mesothelial cells getting converted to myofibroblasts with increased production of fibrin.<sup>24</sup> The second hit in the form of recurrent peritonitis cause upregulation of pro-inflammatory cytokines Interleukin 1, 6, 18, TNF-alpha which along with TGF-beta further expand the process of fibrosis. TGF-beta also causes over-expression of matrix metalloproteinase 2 and tissue inhibitor of matrix metalloproteinase 1 that inhibit fibrin degradation and along with vascular endothelial growth factor (VEGF), PDGF, fibroblast growth factor (FGF) lead to encapsulation and cocoon formation.<sup>21,23,24</sup>

## Pathology

The gross appearance is of a cocoon like encasement of the intestine. Three types of abdominal cocoon have been described based on the extent of involvement of the small intestine or other organs. If the membrane involves only a part of small intestine the cocoon is of type I, if the entire small bowel is involved it is the type II and if the colon or any visceral organs are also encapsulated then it is of type III.<sup>8</sup>

Recently, a type IV cocoon has been described with neuroendocrine tumors where in the entire peritoneum lining the abdominal cavity is involved by the cocoon.<sup>15</sup> However, this can also be regarded as an advanced type III cocoon. On histological examination the membrane shows lamellar matrix of fibrin suggesting that it is derived from the fibrin that has exuded during the “first hit”. The evidence for the “second hit” can be appreciated in form of blood and inflammatory cell infiltrate from recurrent peritonitis.<sup>2</sup>

## Clinical presentation

It is encountered equally in both genders and presents over a wide age range of ages from young as well as

very old with oldest patient reported of 90 years.<sup>5,6,25,26</sup> The hallmark of EPS is the intermittent nature of its presentation. The initial symptoms are usually related to the altered gut motility and transit and altered peritoneal permeability. With the development of complete sclerosis due to formation of cocoon there are overt signs of intestinal obstruction (partial/ complete). A retrospective Japanese study proposed four stages of EPS in the setting of PD.<sup>27</sup> The stage I is the pre-EPS stage where in due to increased peritoneal permeability patient develops ascites with hypoproteinemia. The Stage II presents with signs and symptoms of inflammation from bacterial or chemical peritonitis and the patient presents with fever, loss of appetite, loss of weight, fatigue, ascites with increase in acute inflammatory markers like ESR and CRP. With repeated attacks of stage II, the stage III sets in with progressive encapsulation with small intestinal obstruction and presents with abdominal pain, nausea, vomiting, constipation, and ascites with or without abdominal mass with signs of severe malnutrition. Finally after years, the stage IV sets with formation of cocoon and patient presents with complete ileus and abdominal mass. Since this description is primarily in the setting of PD, all stages are not likely to be seen in patients with other underlying etiological factors and is not uncommon for these patients to present directly in complete intestinal obstruction. Besides these features, patients may have telltale signs of the underlying etiology. **Table 2** lists the important series that report about non-CAPD related cases of abdominal cocoon.<sup>5,6,25,28-31</sup>

In patients undergoing peritoneal dialysis, encapsulating peritoneal sclerosis can be suspected in early stages when there is a hemorrhagic effluent from PD catheter or when elevated levels of inflammatory mediators and markers of the coagulation-fibrinolysis system such as interleukin-6 and fibrin/fibrinogen degradation products are raised.<sup>32</sup>

## Evaluation

The diagnosis of cocoon abdomen has to be suspected in appropriate clinical setting taking into account past medical and surgical history, along with findings on radiology. Although the idiopathic form of disease

**Table 2: Important series on non-peritoneal dialysis related abdominal cocoon in English literature (10 patients)**

Reference	No	M:F	Age (years)	Etiology	Clinical Presentation	Duration of Symptoms	Treatment	Postoperative complications	Mortality	Type of Cocoon
Célicout B Dig Surg1998	32	18:14	56.3 (19-85)	Idiopathic: 5, Postsurgery: 19, $\beta$ -blocker: 4, Cirrhosis: 3, CAPD: 3, Generalized peritonitis: 3	IO: 28, Mass: 8, Asymptomatic: 1	NA	Membrane resection: 5 Adhesiolysis: 12 Resection: 7 Only laparotomy: 8	Intestinal wound: 6, Postoperative leak: 7, Persistent Obstruction: 2	Early: 6 Overall: 16	NA
Wei B et al 2009	24	9: 15	34 (15-57)	Idiopathic	IO: 21 Mass: 13	3d-18 years	Adhesiolysis: all, Resection: 2, Cecofixation: 2, Plication of SIT: 1	Recurrent IO: 6 Fistula: 1	None	I: 14 II: 6 III: 4
Liu HY et al 2009	12	7: 5	43 (8mo - 78)	Idiopathic	IO: 12 Mass: 10	NA	Excision capsule: 8, Adhesiolysis: 8, Drain: 3, Resection: 1	None	None	I: 2 II: 0 III: 10
Wani I et al 2010	11	3: 8	18.3 (16 mo - 58)	Tuberculosis	IO: 11	NA	NA	Recurrent obstruction: 1	None	III: 1
Singh B et al 2013	18	10: 8	(16-70)	Idiopathic: 9 Tuberculosis: 9	IO: 2, Perforation peritonitis: 16, Lump: 2	15 d- 2 years	Adhesiolysis: 17 Ileostomy: 2	None	One (not operated)	NA
Li N et al 2014	65	57: 8	39 (14-79)	Idiopathic: 46 Postoperative: 19	IO: 53 Mass: 21	3.9 $\pm$ 6.72 years	Adhesiolysis: all Resection: 2 Stenting: 23	Early IO: 18 Recurrent IO: 4	None	I: 34 II: 15 III: 15
Li M et al 2014	44	36: 8	44 (19-70)	Idiopathic: 23 Postoperative: 21	IO: all	NA	Adhesiolysis: all Resection: 6 Tube splinting: 11	Early IO: 3 Total IO: 6	None	I: 13 II: 31

was initially recognized only in post-menarche female patients, now primary idiopathic variant is recognized to occur in any age and gender while several secondary causes of EPS are also recognized.<sup>1,8</sup> A study also reported a set of clinical features to identify cocoon preoperatively. These were: intestinal obstruction in a young girl without a definite etiology, presentation with abdominal pain and vomiting but no definite obstruction, history of previous spontaneously resolving episodes of obstruction and presentation with soft non tender abdominal lump.<sup>33,34</sup> These may not hold true for the patients with secondary EPS or even for all patients with primary EPS. **Table 1** lists various etiologic factors that must be sought in a patient with abdominal cocoon.

## Radiological evaluation

Various radiological modalities employed for diagnosis are abdominal X-rays, ultrasonography (USG), small bowel barium studies, contrast enhanced computed tomography (CECT) and contrast-enhanced magnetic resonance imaging (MRI).<sup>6,35-37</sup> These may help in establishing a convincing preoperative diagnosis in most (but not all) cases.

On abdominal X-rays, dilated small bowel loops with multiple air fluid levels with clumping of bowel loops in center of abdomen may be seen, but the sensitivity is low.<sup>5,38</sup> Peritoneal and bowel wall calcification has been also reported.<sup>39</sup> Ultrasonography (USG) in abdominal



cocoon may show dilated small bowel loops fixed to posterior abdominal wall, trilaminar appearance of bowel wall, ascites with or without loculations, a membrane covering the small bowel loops with occasional formation of a mass of bowel loops and adhesions. On USG clumped bowel loops appear to be in “concertina shape” attached with a narrow mesentery giving appearance like a “cauliflower”.<sup>40,41</sup> Ultrasound may be limited by gas in the bowel and is operator dependent. USG may also show “sandwich appearance” due to the presence of echogenic membrane around the bowel loops.<sup>42</sup> On small intestinal barium series, small intestine loops appear clumped towards center of abdomen because of membrane formation and appear like a cauliflower or accordion - first described by Navani in 1995.<sup>40,43,44</sup> There may also be prolonged transit time and in cases presenting with acute obstruction contrast studies may not be possible.<sup>45</sup>

Computed tomography (CT) of abdomen has a sensitivity of 73-95% to detect etiology of high grade small bowel obstruction.<sup>46</sup> It is the most important modality short of surgery which helps in diagnosing the disease, delineating the extent of involvement and associated complications and helps in guiding management. The characteristic feature is conglomeration of small bowel loops in center encased by dense capsule and relatively contrast free periphery. CT may show ascites, loculated fluid collections, peritoneal and mesenteric thickening, features of intestinal obstruction, small bowel thickening, lymphadenopathy, mural or peritoneal calcifications.<sup>5,34</sup> Calcification occurs around the blood capillaries and may extend into the serosal and muscular layers.<sup>47</sup> The characteristic appearance of tethered small bowel loops because of retraction of the mesentery has been described as “gingerbread man” sign.<sup>48</sup> Also, cauliflower sign is also described on CT (**Figure 1**). The distinctive findings on CT described in EPS secondary to peritoneal dialysis are peritoneal thickening (100%), loculated fluid collection (90%), calcification (70%), congregated small bowel loops in the center of the abdomen (60%) and peritoneal enhancement (50%).<sup>39</sup> On CT it may not be always possible to see the fibrous capsule especially when it is thin.<sup>49</sup> CT scan in addition to accurately diagnosing the condition also rules out other differentials. In peritoneal

encapsulation CT scan may reveal helical pattern of small bowel loops displaced anteriorly suggestive of “Helix sign” helpful in identifying peritoneal encapsulation as a differential of EPS.<sup>50</sup>

Magnetic resonance imaging (MRI) has been recently reported as another useful modality in diagnosing EPS. The authors noted no significant difference between MRI and CT, moreover encasing membrane was more obvious in MRI with definite advantage of no exposure to ionizing radiation.<sup>37</sup> Recently use of “cine MRI” has been reported in diagnosis of cocoon in patients on chronic peritoneal dialysis where it was seen that that bowel movements in these patients, are confined to some areas of the abdomen.<sup>51</sup>

### Differential diagnosis

In any patient presenting with features suggestive of intestinal obstruction, possibility of (i) extra-luminal causes (extraintestinal or intramural) like: adhesions, masses (appendicitis, diverticulitis, peritoneal carcinomatosis, neuroendocrine tumor, lymphoma), strangulation, hernia, malrotation and (ii) intraluminal causes like: intestinal tuberculosis, Crohn’s disease, intussusception, radiation enteropathy, bezoars need to be considered. The disease processes with similar imaging features like cocoon are internal hernia, pseudomyxoma peritonei, peritoneal carcinomatosis, peritoneal mesothelioma, sclerosing malignant lymphoma and malignant primary mesenteric tumors.<sup>5,6,48</sup>

Patients, especially in areas with high prevalence of tuberculosis, should be evaluated with chest X-ray, sputum for AFB, skin PPD, erythrocyte sedimentation rate, ascitic fluid analysis including adenosine deaminase, serum ACE levels. Tubercular peritonitis may occur in three forms - wet, dry or fibrotic. CT in wet form will have ascites, which may be loculated. In fibrotic type matted bowel loops are seen with mesenteric nodules. In dry type there are fibrous adhesions and mesenteric thickening. Abdominal lymphadenopathy is another characteristic feature. **Table 3** shows the various differential diagnosis of abdominal cocoon.<sup>52-57</sup>

**Table 3: Differentials of abdominal cocoon on imaging**

Differential	CT Features
Tubercular peritonitis	Wet type: Diffuse, hyper-attenuating ascites which may be loculated. Fibrotic type: Matted bowel loops are seen with mesenteric nodules. Dry type: Fibrous adhesions and mesenteric thickening is seen. Characteristic abdominal lymphadenopathy is another distinguishing feature.
Internal hernia	CT shows centrally located, clustered small bowel loops, with displacement of surrounding organs, stretching of mesenteric vessels and features of small bowel obstruction. However, no membrane like sac present.
Peritoneal mesothelioma	Peritoneal mesothelioma also has three forms - wet, dry and mixed. Wet type: Ascites with intestinal obstruction secondary to diffuse nodules and plaques. Dry type: large abdominal mass or multiple nodules may be present in the absence of ascites. Other features include scalloped margins of viscera, invasion of solid organs and omental mass.
Peritoneal carcinomatosis	CT shows low attenuation mucinous ascites with amorphous calcifications scalloping the margins of liver and spleen. On USG gelatinous fluid is seen pushing the bowel centrally giving sunburst appearance.
Peritoneal encapsulation	In this condition an accessory peritoneal sac covers the entire small bowel without being adherent to small intestinal loops.
Encapsulating Peritoneal Sclerosis	On CT: there is variable diameter of bowel segments, adherent dilated loops, features of obstruction, loculated ascites, thickened intestinal wall and peritoneal membrane, increased density of mesenteric fat, entrapped fluid collection and peritoneal calcification are seen. On USG echogenic membrane has been described to have “sandwich appearance”

## Management of abdominal cocoon

### Prevention of EPS

The duration of CAPD is the most important risk factor which predisposes to occurrence of EPS in patients with chronic kidney disease on peritoneal dialysis. Also, repeated episodes of peritonitis, the type of peritoneal fluid used, faster peritoneal membrane transport, age at which PD was started, diminishing ultrafiltration and renal transplantation are recognized as other risk factors.<sup>58</sup> Since the consequences of EPS are devastating with high mortality rates, it is important to recognize and prevent this complication. Diminishing ultrafiltration may identify the subset of patients likely to develop EPS and may benefit from stopping PD. However, this needs to be confirmed on prospective studies and it may be worthy to recognize the role of bio-compatible fluids and concomitant use of anti-fibrotic agents in prevention of EPS. Preemptive

use of tamoxifen in patients with PD related peritoneal sclerosis vis-à-vis no treatment reduced the occurrence of the advanced EPS and therefore seemed to reduce mortality related to EPS. This suggests that pre-emptive tamoxifen may be considered in patients with PD related peritoneal sclerosis who have not yet developed complete encapsulation.<sup>59</sup>

### Correction of underlying etiology

If the underlying cause is related to use of peritoneal dialysis, cessation of peritoneal dialysis and shifting to hemodialysis should be done. Removal of PD catheter should be considered, however occasionally withdrawal of PD may worsen the EPS.<sup>58</sup> Also, cessation of PD does not entirely eliminate the risk and EPS may occur even after renal transplantation.

Similarly, the institution of anti-tubercular therapy may help in resolution/abatement of cocoon formation

in tubercular abdominal cocoon (TAC). However, most available literature reports the use of surgical therapy to treat TAC and evidence regarding use of ATT alone or with immunosuppressive drugs like steroids is limited. In drug related EPS, discontinuation of drug may be beneficial.

### Medical therapy

Several reports describe the use of various pharmacological agents for treatment of EPS. The agents used include steroids, mTOR inhibitors and tamoxifen. Corticosteroids have immunosuppressive and anti-inflammatory properties, which may be responsible for the benefit they exert in management of EPS. Multiple reports indicate the utility of steroids as a sole agent and in combination with other immunomodulators and with tamoxifen in management of EPS related to PD. Steroids are also beneficial for treatment of post-renal transplant EPS.<sup>60</sup>

Tamoxifen is a selective estrogen receptor modulator (SERM) which has been reported to be of utility in therapy of EPS related to peritoneal dialysis. The benefit may be mediated by non-ER dependent mechanisms including modulation of TGF-beta related pathways.<sup>58</sup> Tamoxifen is also recognized to be of utility in management of other fibrosing disorders like sclerosing mediastinitis, retroperitoneal fibrosis.<sup>58</sup> However, these patients also received surgical intervention in form of laparotomy with or without adhesiolysis.<sup>61</sup> In a large retrospective Dutch study, the subgroup of patients who received tamoxifen had a significantly lower mortality than those who did not receive the drug.<sup>62</sup> Some reports do suggest the benefit of tamoxifen monotherapy in doses of 10-40 mg/day. The fact that tamoxifen has no immunosuppressive action makes it convenient to use in most clinical situations.<sup>63</sup>

In a recent review of published case series and reports, the use of inhibitors of mechanistic target of rapamycin (mTOR) like everolimus was reported in 20 patients with PD related encapsulating peritoneal sclerosis and suggested some benefit to patients who had developed EPS after renal transplant, possibly due to the fibrotic action of calcineurin inhibitors.<sup>64</sup> In another report, EPS was detected at a mean of 10.5 months after

renal transplantation and of the 10 patients with post-transplant EPS, 5 were treated with mTOR inhibitors and four had a positive outcome.<sup>65</sup> Therefore, a change from calcineurin inhibitors (CNI) to mTOR inhibitors may be considered in patients who develop EPS after renal transplantation.<sup>64</sup> However, most reports have used the drug usually in combination with steroids and/or surgery. It is uncertain if use of medical treatment alone can suffice. The evidence regarding other immunomodulators is even less convincing. There is some experimental evidence from animal studies and occasional case reports that mycophenolate mofetil and azathioprine may have a role in treatment of EPS, however firm clinical evidence is lacking.<sup>66</sup> There is also evidence that CNI (cyclosporine and tacrolimus) may increase the risk of EPS. The increasing recognition of post renal transplantation EPS suggested that lowering of steroid dose and use of profibrotic CNI may have contributed to the trend.<sup>67</sup> The patients who develop post-transplant EPS may benefit by decreasing or eliminating the CNI.<sup>64</sup> A report also suggests that use of far-infrared therapy, through anti-inflammatory action and stimulation of neoangiogenesis and improved endothelial function through eNOS and HO-1, may improve EPS.<sup>68</sup>

In spite of growing evidence of the utility of these agents in treatment of PD related EPS, the evidence in other forms of cocoon is virtually non-existent. Also, these pharmacological agents have often been used in varying combinations and in conjunction with surgical therapy. Therefore, no firm recommendations are possible regarding the dosage, duration and combination in which they may be used, especially in a non-PD EPS setting.

### Surgical treatment

Traditionally in EPS, surgery has played both diagnostic and therapeutic role as has been seen in various series that most of the patients were diagnosed intra-operatively.<sup>5,6,30</sup> The most widely used surgical procedure is complete resection of membrane and wherever possible adhesiolysis should be performed cautiously avoiding inadvertent bowel injury. In case of injury during stripping and adhesiolysis the proximal most part of the intestine is exteriorized till recovery. Intestinal resection

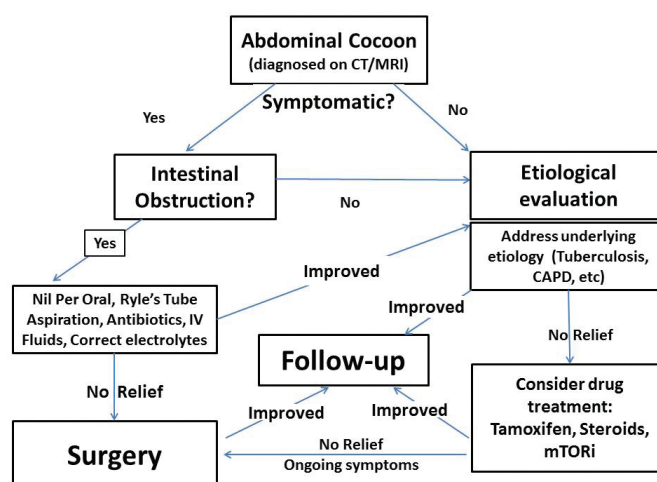


is only performed in non-viable gut but there are very high chances of post-operative fistula formation. To prevent post-operative recurrent obstruction, intestinal intubation or plication can be done retrograde through the appendicular orifice avoiding acute angulations, which also helps to minimize fistula formation.<sup>5,31</sup> A good preoperative nutritional support, enteral or parenteral, reduces post-operative complications, hospital stay and time to oral intake.<sup>5</sup>

With the increasing awareness of the condition, pre-operative diagnosis can be made with help of CT scan with findings in the form of peritoneal thickening, calcification and enhancement, loculated ascites and bowel obstruction. However, these are findings seen in the advanced stage of the disease where the prognosis is poor with high mortality.<sup>69</sup> CT scan has a poor sensitivity in picking up the early membrane changes before EPS has formed and hence the role of laparoscopy in a patient presenting with recurrent abdominal pain with a background of known risk factors. Laparoscopy may show early changes of EPS in the form of peritoneal tanning and brown leathery appearance. With the use of tamoxifen, azathioprine and steroids the above finding have been shown to resolve with normalization of peritoneum.<sup>69</sup> A recent report from India suggests that the use of antitubercular therapy in patients with tubercular abdominal cocoon may help avoid surgery in a subset of patients.<sup>70</sup> **Figure 3** depicts the suggested management strategy for patients in whom abdominal cocoon is recognized pre-operatively.

### Future targets

The key to avoiding the formation of abdominal cocoon may lie in the prevention of epithelial-to-mesenchymal transition of the mesothelial cells of the peritoneum. This might avoid the genesis of peritoneal fibrosis consequent to peritoneal infection and/or inflammation. Various agents which have been tested in preclinical studies and may have anti-fibrotic properties include melatonin, rapamycin, pirfenidone.<sup>70-72</sup> Blockage of toll like receptors 2 and 4 have been proposed as potential therapeutic targets for PD associated peritoneal sclerosis as these are responsible for mediating the pro-fibrotic response in relation to infection and/or inflammation.<sup>73</sup> Other reported mediators for the



**Figure 3:** Flow chart showing suggested management approach for patients of abdominal cocoon diagnosed preoperatively.

fibrogenic response include angiotensin II receptors, vascular endothelial injury.<sup>74</sup> A study in mouse model has suggested the role of beta-blocker nebivolol in preventing peritoneal dialysis induced fibrogenic responses.<sup>75</sup> Other drugs and agents which have been found to have some benefit in animal studies include rosiglitazone, N-acetyl cysteine, colchicine, angiotensin inhibition, thalidomide as well as biocompatible PD solutions.<sup>60</sup> However, the translation of these experimental evidence into clinical practice is awaited.

In conclusion, EPS is an enigmatic clinical entity which may result from a myriad of conditions and needs to be identified early to possibly delay the progression and avoid surgery. However in patients with unremitting symptoms and intestinal obstruction surgery remains the cornerstone to management.

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