Peritoneal Adhesions and Encapsulating Peritoneal Sclerosis

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Key Points

1. Adhesions are common after abdominal surgery and up to 5% will need a repeat admission for them. The chance of developing them increases with the number of abdominal operations.
2. Adhesions/intraperitoneal fibrosis may be caused by ischaemia, infection, abrasions, spillage of gastrointestinal contents, desiccation, excessive heat/light/electrocautery/sutures, fibres/glove powder and some medications. Reducing these factors reduces the chance of developing adhesions.
3. Adhesions may cause recurrent episodes (partial or complete) of bowel obstruction. These episodes may be reduced by a low fibre diet. They may also be associated with infertility.
4. Adhesions and adhesion-related readmission to hospital are more common after open than laparoscopic surgery
5. Topical agents reduce the formation of adhesions but have not been shown to reduce readmissions or reoperations for adhesions.
6. Encapsulating peritoneal sclerosis (EPS) is the most severe form of adhesions and may cause a frozen abdomen on which surgery is very difficult.
7. Patients with adhesions/EPS are encouraged to chew their food well before swallowing. A low insoluble fibre/low residue diet can reduce the chance of obstructive symptoms occurring.

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Adhesions

What Are They?

Adhesions in the peritoneal cavity are non-anatomical attachments between visceral and/or parietal peritoneal surfaces. They can be congenital or acquired. Congenital adhesions can range from complete peritoneal encapsulation, a rare cause of bowel obstruction in children and adults, to congenital bands that can cause internal herniation and volvulus. Studies reveal that 5–27% of those who have never had abdominal surgery have abdominal adhesions [1, 2]. This prevalence increases with age, suggesting that adhesions often form secondary to abdominopelvic events such as diverticulitis [2].

Adhesions are most prevalent in people who have had previous surgery. Prospective data from the pre-laparoscopic era demonstrated that the prevalence of adhesions in people undergoing laparotomy increased from 11.5% in people who had not undergone previous surgery to 93% in those who had [2]. Most of the adhesions noted had formed between the greater omentum and the abdominal wall scar.

Histological studies of postoperative adhesions reveal that they are typically collagenous bands initiated either by peritoneal injury or bleeding or a combination [1]. In the past, foreign bodies were the dominant cause of postoperative adhesions, but this has likely diminished as talcum powder, starch and textile materials have become replaced by safer materials [1].

Additional causes of acquired adhesions between surfaces in the peritoneal cavity include neoplasia, endometriosis, radiotherapy and a range of infections such as chlamydia and tuberculosis.

J. M.D. Nightingale (ed.), *Intestinal Failure*, https://doi.org/10.1007/978-3-031-22265-8_8

Adhesions in the Context of General Surgery

Peritoneal adhesions play a role in the pathogenesis of an array of symptoms and conditions of affected organ systems. Gastrointestinal and gynaecological complaints are the most common. Here, we will focus on complaints seen in general surgery that may or may not be associated with adhesions.

Abdominal Pain

Chronic or recurring abdominopelvic pain is common after abdominal surgery and adhesions are often thought of as an important cause of such symptoms. However, the evidence linking adhesions themselves and pain is poor. There is supportive experimental evidence, such as the findings of sensory nerve fibers in adhesions [3, 4].

It is not straightforward to scientifically study the role of adhesions as a cause of symptoms, as intraperitoneal adhesions are so prevalent in the population [2]. We instead have to rely on studies of adhesiolysis to examine this role. In a landmark study from the Netherlands, 100 patients with long-term abdominal pain after laparotomy underwent diagnostic laparoscopy and, if adhesions were found, randomised to laparoscopic adhesiolysis or no further dissection [5]. Three to 12 months after laparoscopy, pain scores decreased in both study groups, with no differences between groups. This suggests a placebo effect, and no additional effect of adhesiolysis on pain.

Seventy-three patients were then followed up at 12 years [6], and at this timepoint significantly worse outcomes were found in the group that had undergone adhesiolysis, including more frequent pain and use of analgesics and, perhaps most significantly, an increased number of reoperations to address adhesions.

Thus, while it remains possible that adhesions cause abdominal pain, adhesiolysis has no benefit in the short term, and an adverse impact in the long term, on this symptom. It should be avoided as a therapy for pain alone.

Intestinal Obstruction

It is clear that peritoneal adhesions, whether congenital, postoperative or otherwise acquired, are a dominant cause of small bowel obstruction: meta-analysis suggests that 56% of cases are caused by adhesions [7].

The magnitude of the problem of postoperative adhesions has been extensively studied in the so-called SCAR studies, registry studies that followed large cohorts who had abdominal surgery in Scotland. In the SCAR-1 study, 29,790 patients who underwent laparotomy in 1986 were retrospectively studied for 10 years [8]. One in three patients were readmitted to hospital during this time period. Most were readmitted more than once, resulting in a total number of readmissions of 21,347. Of those readmissions, 5.7% were documented as being caused by adhesions, in most cases by findings at surgery. In a much larger number of readmissions, 38% of the 21,347, adhesions were judged to be "possibly" causative based on a set of criteria. The SCAR-1 study established that readmission to hospital after open abdominal surgery is common and frequently directly or possibly caused by adhesions. The subsequent SCAR-2 study assessed changes during the time period 1996–1999, observing no change in the risk of readmission after open abdominal surgery [9].

The SCAR-3 study further analysed a cohort operated in the financial year 1996 with regard to types of index surgery [10]. The risk of readmission for documented adhesions during the subsequent 5 years was 3.8% for the whole cohort, and 5.2% excluding appendectomy. The risk was particularly increased following panproctocolectomy (15.4%), total colectomy (8.8%) and ileostomy procedures (10.6%) and decreased following small bowel surgery (1.8%) and appendicectomy (0.9%) [10]. The risk in patients who previously had had open abdominal surgery was twice that of those who had not. Although multivariable analyses were not performed, univariable analyses suggested that increasing age appeared to protect against readmission for adhesions, and Crohn's disease did not change the risk [10].

The concept that some patients form adhesions more readily than others is supported by long-term follow-up in the LAPAD study from the Netherlands [11]. In this study of 604 patients who had elective abdominal surgery in a single centre from 2008 to 2010, 32% were found to have severe adhesions, mostly from previous laparotomies, while 68% had mild or no adhesions. During a relatively short median follow-up of 46 months, 38 of the 604 (6.3%) re-presented with adhesive bowel obstruction. On multivariable regression, the finding of severe adhesions at index surgery was a strong predictor of subsequent adhesive small bowel obstruction [11].

In summary, some 60% of cases of small bowel obstruction are caused by adhesions, and in the long term of 4–10 years, at least 5% of patients undergoing abdominal surgery will be readmitted with proven adhesive bowel obstruction. Of note, these data are from cohorts of patients who nearly all underwent open surgery. The impact of minimally invasive surgery on adhesion-related morbidity is examined below.

Morbidity During Future Operations

Another consequence of adhesions is lengthy adhesiolysis during future intraperitoneal operations. This is not only time-consuming, but is associated with increased morbidity. The initial LAPAD study focused on adhesiolysis as a risk factor for adverse outcomes [12]. In this prospective study, 755 elective open or laparoscopic abdominal operations were observed. Adhesiolysis was required in 475 operations, and in 50 of those (10.5%) an accidental enterotomy was made. Adhesiolysis added a median of 20 (range 1–177)

minutes to the operation. The risk was of enterotomy was particularly increased in operations requiring more than an hour of adhesiolysis. In the 280 operations during which adhesiolysis was not required, no enterotomies were made. The difference in enterotomy risk helps explain several associations between adhesiolysis and adverse outcomes seen in this study, such as postoperative sepsis, increased length of hospital stay and increased costs [12].

Cost to Healthcare Services

Calculating the economic costs of adhesions is complicated as it encompasses the costs of clinic and emergency visits, diagnostic tests, hospital admissions, surgery performed to treat adhesions, adhesiolysis during other peritoneal surgery, loss of income from admissions, and other costs.

The LAPAD study estimated that the mean hospital cost for each patient undergoing elective surgery increased from USD 14,063 in those without adhesions to USD 18,579 in those with adhesions in the Netherlands in 2010 [12].

A Finnish population-based study estimated that, at 1999 currency levels, annual direct hospital for small bowel adhesion in the country was GBP 2,077,796, similar to the costs of treating rectal cancer throughout the country [13].

Adhesions in the Context of Intestinal Failure

Although extensive peritoneal adhesions have long been recognised as a cause of intestinal failure [14], data on this association are scarce. In the largest published series of long-term (3 months or longer) parenteral nutrition, mechanical obstruction was the mechanism of intestinal failure in 20/545 (3.7%) of patients treated at the Irving National Intestinal Failure Unit in Manchester, UK during the period 1978–2011 [15]. In a snapshot study from the same unit in 2017, the proportion was 15/273 (5.5%) cases [16]. However, these studies included patients with cancer as the underlying diagnosis, and the number of patients with benign adhesions is likely to be less.

Given the prevalence of peritoneal adhesions in the population, the risk of developing intestinal failure through this mechanism can reasonably be assumed to be small. Empirically, cases where benign adhesions are the dominant cause of intestinal failure are unusual. Where this occurs, adhesions are often the result of multiple operations, previous peritonitis and/or implanted mesh.

A much more common clinical challenge is the patient with small bowel dysmotility who has previously undergone surgery, often subtotal colectomy for suspected slow-transit constipation. Such patients frequently have radiological findings consistent with both intestinal dysmotility and adhesive obstruction. Assessing the contribution of adhesions in such cases is crucial in order to predict the likelihood that surgical adhesiolysis will improve intestinal function. Helpful tools in this assessment include longitudinal imaging to identify any fixed transition points, histopathology with specific immunohistochemistry on full-thickness small bowel samples to identify known dysmotility disorders such as visceral myopathy [17], and in selected cases a trial of a loop enterostomy proximal to a suspected obstructive site to assess whether function in the proximal small bowel normalises.

Diagnosis

Diagnosing Adhesions

In the absence of concurrent small bowel obstruction, adhesions in the peritoneal cavity are not visualised by static radiological imaging such as computed tomography or magnetic resonance imaging. However, dynamic ultrasonography is emerging as a promising diagnostic modality, in particular in the obstetric field. In the so-called visceral slide test, the viscera are visualised by ultrasound in different regions of the abdomen, and the extent of movement in response to normal or forced respiration is assessed. Restricted or absent movement, or slide, is thought to reflect peritoneal adhesions. A recent meta-analysis of 25 observational studies focused on the periumbilical area, commonly used for laparoscopic access to the peritoneal cavity [18]. A positive predictive value of 60.4% and, more importantly, a negative predictive value of 99.2% was demonstrated [18]. The gold standard used in these studies was the findings on laparotomy or laparoscopy. While this finding has implications for minimally invasive surgical techniques, better data are needed on visceral slide sonography in the rest of the abdomen.

Abdominal dynamic magnetic resonance imaging, or cine-MRI, is a similar technique that has been evaluated with promising results [19]. In a head-to-head comparison, dynamic ultrasound and MRI both performed well, and cine-MRI was superior in detecting adhesions between viscera such as small bowel [20].

Dynamic imaging is yet to enter routine clinical practice, but the techniques are available and could prove valuable in investigating unclear symptoms or preparing for complex abdominal re-operative surgery. The gold standard in diagnosing adhesions remains direct visualisation at surgery. During surgery it is also possible to systemically assess and grade adhesions (Fig. 1). Several scores have been proposed. The Zühlke score described in 1990 is based on the histopathology of adhesions, grading them from weak to thick [22]. The increasingly used peritoneal adhesion index (PAI) instead describes the severity of adhesions in the regions of the abdomen, and provides a summative score (Fig. 2) [23]. In brief, adhesions observed at surgery are scored 0 (no adhesions)–3 (very strong vascularised adhesions). The

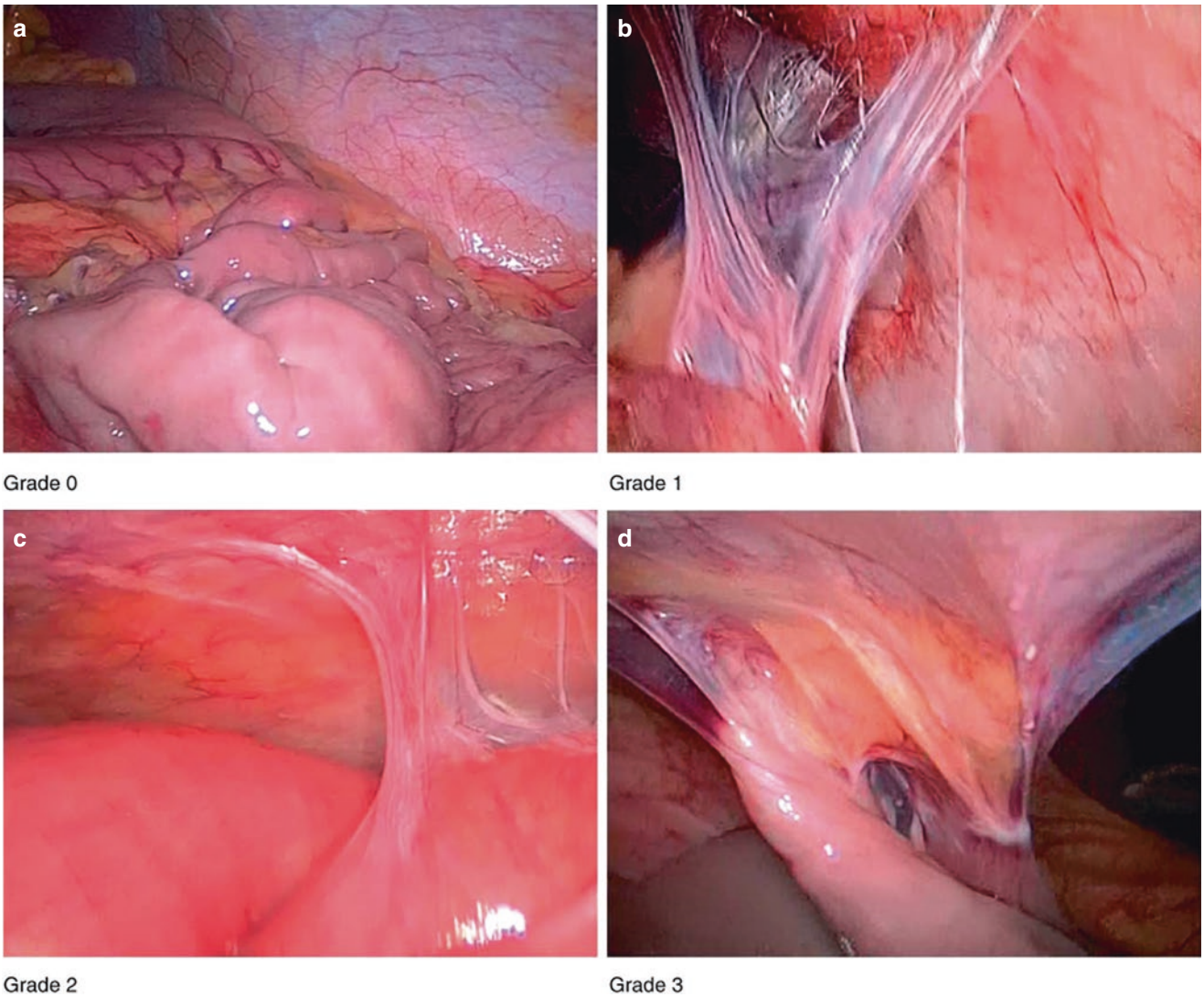


Fig. 1 Severity of adhesions. (**a**) no adhesions (grade 0); (**b**) flimsy thickness, avascular (grade 1); (**c**) moderate thickness, limited vascularity (grade 2); and (**d**) dense thickness, vascularized (grade 3). (Hull et al., Adhesions after laparoscopic and open ileal pouch–anal anastomosis surgery for ulcerative colitis, Br J Surg, 2012, 99(2);270–5, by permission of Oxford University Press [21])

abdomen is divided in nine even regions, and adhesions in each region are scored on this scale. A tenth score is determined for inter-loop adhesions. The ten scores are added up and the sum is the total PAI score.

Diagnosing Adhesive Intestinal Obstruction

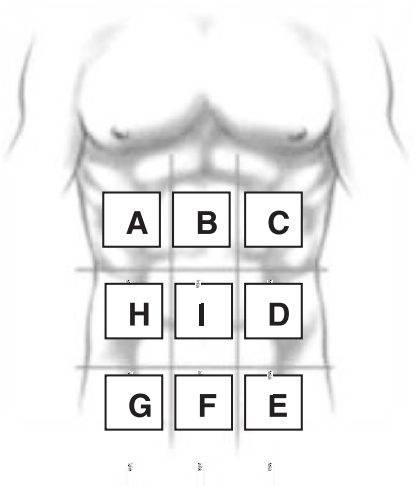
When adhesions are complicated by concurrent intestinal obstruction, the clinical presentation and radiological findings are more sensitive and specific. The patient often presents with a sudden onset of colicky central abdominal pain which is worse in the ileum than jejunum and may follow eating a fibrous/grisly bit of food (often not well chewed). This may be followed by vomiting, a yellow/green vomit suggest proximal small bowel obstruction and a dark brown fluid a more distal one. The bowel/stoma may stop working. The abdomen may be distended with loud bowel sounds. If an obstruction resolves it is followed for 1–3 days by diarrhoea or if a stoma a high output.

Useful radiology includes plain abdominal X-ray and cross-sectional imaging, and findings include dilated small bowel up to the point of obstruction (diameter above 3 cm), air–fluid levels and an absence of gas in the colon. Cross-sectional imaging often confers additional information, such as the cause of obstruction and can show signs of ischaemia.

A difficulty arises when a patient presents with intermittent symptoms suggesting small bowel obstruction. Ensuring that urgent diagnostic imaging is obtained before symptoms resolve is the only way to diagnose obstruction in such cases.

A similar problem is posed when diagnosing low-grade small bowel obstruction. Such relative obstruction may not

PERITONEAL ADHESION INDEX:



Regions:	Adhesion grade:	Adhesion grade score:
A Right upper	____	**0** No adhesions
B Epigastrium	____	**1** Filmy adhesions, blunt dissection
C Left upper	____	**2** Strong adhesions, sharp dissection
D Left flank	____	**3** Very strong vascularized adhesions, sharp
E Left lower	____	dissection, damage hardly preventable
F Pelvis	____	
G Right lower	____	
H Right flank	____	
I Central	____	
L Bowel to bowel	____	

PAI ☐

Fig. 2 Peritoneal Adhesion Index (adapted from Coccolini et al. [23]). Each area of the abdomen is ascribed an adhesion related score. The sum of the scores will result in the PAI

result in pre-stenotic dilatation, resulting in a sensitivity of CT in this condition of only 50% [24]. Enteroclysis, in which contrast is delivered directly into the small bowel at a high rate through a nasojejunal tube, is more sensitive to detect low-grade obstruction; indeed, some studies suggest the technique is near 100% sensitive [25].

Prevention

The literature reviewed above shows that surgical adhesiolysis is followed by formation of new adhesions. There is currently no other treatment of adhesions. Therefore, prevention in routine surgical practice is a crucial priority to reduce the considerable morbidity and costs associated with adhesions.

Surgical Technique

Several surgical techniques have been proposed to decrease adhesion formation following intraperitoneal surgery (Table 1). They include minimally invasive approaches; closure of the parietal peritoneum; avoidance of foreign bodies such as glove powder, sutures and meshes; prevention of infection; and peritoneal lavage. A 2012 meta-analysis found no effects of such techniques on rates of subsequent clinically significant adhesions or adhesions on subsequent surgery [26].

In regards to minimally invasive surgery, however, the amount of high-quality data has matured further since this meta-analysis. There is now high-grade evidence that supports the hypothesis that laparoscopic surgery significantly decreases subsequent adhesion-related morbidity. The SCAR study group retrospectively studied 72,270 patients who underwent laparoscopic or open abdominal or pelvic surgery in the period 2009–2011 [26]. After 5 years, 1.7% in the laparoscopic cohort vs. 4.3% in the open surgery cohort had been readmitted to hospital with proven adhesion-related morbidity, mainly adhesive small bowel obstruction. Adjusting for confounders, the authors found that laparoscopy reduced the risk of adhesion-related readmission within 5 years of surgery by 32% [27].

Data from the series of large randomised trials that first evaluated safety and efficacy of laparoscopic colon and rectal cancer resection have mostly been unable to demonstrate effects on long-term adhesion-related morbidity [28–30]. One recent randomised trial did demonstrate reduces rates of adhesions in the minimally invasive surgery group [31]. A recent meta-analysis of randomised trials pooled 4656 patients and did not find an association between laparoscopy and rates of adhesion-related morbidity [32]. The lack of effect in randomised trials is not surprising given the low event rate. Very large study groups would be required to definitively demonstrate an effect of laparoscopy on adhesions in a randomised design.

In summary, available randomised trials are small in relation to the event rate of measurable outcomes, and arguably the best evidence available is large clinical registry data. The recent, large SCAR study update provides strong support for the reasonable notion that less tissue damage results in less formation of adhesions.

It is also reasonable to suggest that, regardless of surgical approach, atraumatic surgical technique and meticulous attention to detail is important in preventing adhesion formation, although this factor is difficult to quantify and study. Both tissue injury and bleeding play a role in initiating adhesion formation, and are best minimised. Tissue injury is minimised by focused sharp dissection, avoiding blunt dissection, optimum settings in energy devices, careful retraction of tissues and using inert irrigation fluid at body temperature.

Table 1 Adhesion prevention strategies

Awareness of risk factors
Increasing age
Number of previous laparotomies
Complexity of the procedure
Location of the procedure (increased in pelvic procedures)
Crohn's disease
Resections for colonic cancer
Proctocolectomy, total colectomy, ileostomy
Conservatively treated localised peritonitis (appendicitis, diverticulitis)
Surgical technique
Careful tissue handling
Sharp dissection using sharp instruments
Avoid crushing tissue
Avoid unnecessary dissection
Attention to detail with ligatures
Optimum tissue beyond ligature to reduce ischemic tissue
Avoid excessive redundant ends of non-absorbable tissue
Avoid bowel exposure and desiccation
Avoid drying of tissue, in exposed area with adherence of clot
Use laparoscopic technique if possible
Robotic techniques
Avoid peritoneal suturing during wound closure
Use of physical antiadhesion barriers
Seprafilm® Adhesion Barrier (Cambridge, MA; Genzyme Corporation)
Gore Preclude Surgical Membrane Adhesion Barrier Flagstaff, AZ; Gore and Associates Inc.
Gynecare Interceed Absorbable Adhesion Barrier (Somerville, NJ; Johnson and Johnson)
Adept Solution: Adhesion Reduction Solution (Deerfield, IL; Baxter Healthcare Corporation)
Intercoat (AC AG Group, Kaltenkirchen, Germany)
Fibrin Sheet (TachoComb, Tokyo, Japan)
Antibiosis techniques to reduce bacterial translocation
Mechanical bowel preparation
Antibiotics
Pharmacologic agents (anecdotal and experimental)
Antiinflammatory agents (Steroids, NSAIDS)
Tamoxifen (Synthetic nonsteroidal antiestrogen agent, with antifibrotic properties)
Anticoagulants including heparin, ancrod.
Calcium channel blockers
Vitamin E
Halofuginone

Topical Biochemical Agents

Given the significant prevalence of adhesions following intraperitoneal surgery and their associated morbidity

and costs, their prevention by chemical and pharmacological agents has been a large and active research field. Strategies evaluated include systemic agents such as anti-inflammatory drugs and anticoagulants, and chemicals applied topically in the surgical wound. To summarise this field, to date none has been widely applied in clinical practice.

A Cochrane meta-analysis of randomised and pseudo-randomised trials of topical agents, most recently updated in 2009, concluded that a hyaluronic acid/carboxymethyl membrane reduced the incidence and severity of adhesions as assessed at a second, planned operation months later (Odds ratio 0.15), but did not affect the need for unplanned reoperation for adhesive small bowel obstruction (Odds ratio 0.84) [33]. It cautioned that some data suggested an increased risk of anastomotic dehiscence when the agent was applied near an anastomosis. The hyaluronic acid/carboxymethyl membrane was the only agent for which sufficiently high-quality data were available for meta-analysis [33].

A 2014 meta-analysis included non-randomised studies in addition to randomised trials, and made similar conclusions regarding effects of topical agents on adhesion formation, reoperative rates, and importantly on anastomotic complications [34]. Furthermore, other adverse effects were also evaluated, and found to be no different between treatment and control groups. These included wound healing complications and abscess formation. The latter conclusion has been challenged, however, as a preliminary report of a large observational study was not included [35]. This study of 1885 patients who underwent proctectomy and ileal pouch-anal anastomosis reported an increased incidence of pelvic sepsis in patients treated with hyaluronic acid/carboxymethyl membrane (10.2%) when compared to those who were not treated (6.8%, P 0.016) [36].

In the absence of clinical efficacy, it is difficult to support routine usage of hyaluronic acid/carboxymethyl membranes or any other agents to prevent adhesions. Some centres routinely use the membranes around the two limbs of a temporary diverting loop ileostomy as it traverses the abdominal wall, in order to reduce adhesions when it is taken down some 6–12 weeks later. Such usage appears safe and advantageous. It is also reasonable to consider the agent when reoperating patients with a known capacity to form troublesome adhesions.

Systemic Agents

Non-steroidal anti-inflammatory drugs are the most widely studied but their clinical efficacy is questionable. Corticosteroids have poor efficacy and are associated with immunosuppression and delayed wound healing. Fibrinolytics have a risk of impaired wound healing and/or bleeding.

Management in the Context of Intestinal Failure

While type 3 intestinal failure is rarely attributed solely to intraperitoneal adhesions, they are an important factor in the management of type 2 intestinal failure, specifically in determining the timing of reconstructive surgery. For many reasons discussed extensively in chapter “Acute Surgical Intestinal Failure. Sepsis and Enterocutaneous Fistula(s)”, reconstructive surgery for IF is typically delayed until 6–12 months after the most recent surgery. One of the key considerations is the maturation and, ideally, resolution of adhesions. There is no longitudinal data on these processes, but it is a common clinical observation that reoperative surgery within the first 2–3 months is very technically challenging with dense and often still inflamed adhesions; that reoperative surgery after a period of years is much more frequently straightforward and the adhesions encountered soft and filmy. The difficulty is determining the ideal time point between these extremes when relaparotomy is reasonably safe.

Useful clinical tests are simple inspection and palpation of the abdomen. A soft, flexible abdominal wall is promising. If there is a stoma or an enterocutaneous fistula, it is highly useful to observe its movement when the patient coughs or strains; free movement and a slight prolapse of the bowel is a good sign that the abdominal viscera are not rigidly held in a frozen abdomen. If clinical examination suggests that the abdomen is dense and inflammation not yet resolved, it is best to delay reconstructive surgery and re-evaluate after 6 months.

In type 3 IF, adhesions are often present and the challenge is to assess their relevance. As mentioned above, this is particularly the case in conditions associated with impaired small bowel motility, such as dysmotility syndromes.

Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is the most severe form of adhesions/intraperitoneal fibrosis and is a descriptive abdominal manifestation of a spectrum of aetiologic conditions [37]. A diagnosis of EPS in the current era is considered synonymous with the clinic-pathologic syndrome which is an important morbidity of long-term peritoneal dialysis. All forms of peritoneal sclerosis with or without encapsulation can lead to intestinal dysfunction and eventual intestinal failure. The pathophysiologic mechanism in the different diseases varies depending on the specific aetiology. Clinical manifestations occur when there is the formation of a membrane or peritoneal sclerosis which causes adhesions, between bowel loops, and also between the bowel and the parietal peritoneum, causing restriction of gut

motility. With progression of disease, the gut can become cocooned and completely encased, causing progressive intestinal failure. The biologic processes underlying the individual aetiology, disease progression and presentation are varied and multifactorial and clinical presentations can be subtle and mimic other pathology, leading to delayed diagnosis or late presentations. The overarching clinical picture however is one of GI dysfunction associated with intraperitoneal inflammation associated with progressive nutritional deficiency, eventually leading, if untreated to an acute presentation requiring surgical intervention. On a background of significant associated comorbidity, there may be a high risk of mortality or intestinal failure.

The diagnosis of EPS is often made late and in a large number of cases only at surgery. Early diagnosis requires a knowledge and suspicion of the condition in the clinical context, and is confirmed by combining the clinical history, presentation and imaging, surgical findings and histology. EPS is not a histological diagnosis. Surgery remains the mainstay of treatment, and best results are obtained in centres which have experience with managing this relatively rare condition. However, the overall management is complex, requiring a number of disciplines, with nutritional support and surgery playing a key role in management.

The Peritoneum Structure, Physiology and Function

The peritoneal cavity is a potential space, separating the parietal peritoneum, covering the inner walls of the abdomen and the pelvis and the visceral peritoneum covering the abdominal viscera and the bowel. The surface area of the peritoneum is over 1.8 m^2 in area, with an interface of peritoneal fluid, of approximately 100 mL, which allows lubrication and free movement of the bowel. The fluid is an ultrafiltrate of plasma, providing a frictionless environment for the abdominal organs.

The peritoneal surface is formed of a single layer of cells lining the peritoneal cavity, first described by James Douglas in 1730, and then later called the mesothelium by Binot in 1980. These mesothelial cells are 25 μm in diameter, are derived from the mesoderm and possess both mesenchymal and epithelial characteristics (Figs. 3 and 4).

Physiologically, the peritoneum plays an important role in maintaining the intra-abdominal homeostatic equilibrium. The functions of the peritoneal membrane include, transport of fluid and particulate matter, regulation of leucocyte migration, control of coagulation and fibrinolysis, antigen presentation, synthesis of inflammatory cytokines, growth factors and extracellular matrix for repair. These multiple functions enable the several important clinical therapeutic interventions via the peritoneal cavity, including peritoneal dialysis, chemotherapy and immunotherapy [39]. Kastelein et al. have provided an excellent up to date review of the embryology, anatomy, physiology, pathophysiology and pathophysiology of the peritoneum and peritoneal vasculature [40]. More recently studies suggest that exosomes contribute to peritoneal function, by the intracellular transfer of DNA, mRNA, proteins, and lipids. They are thought to play a part in regulating peritoneal membrane function [41].

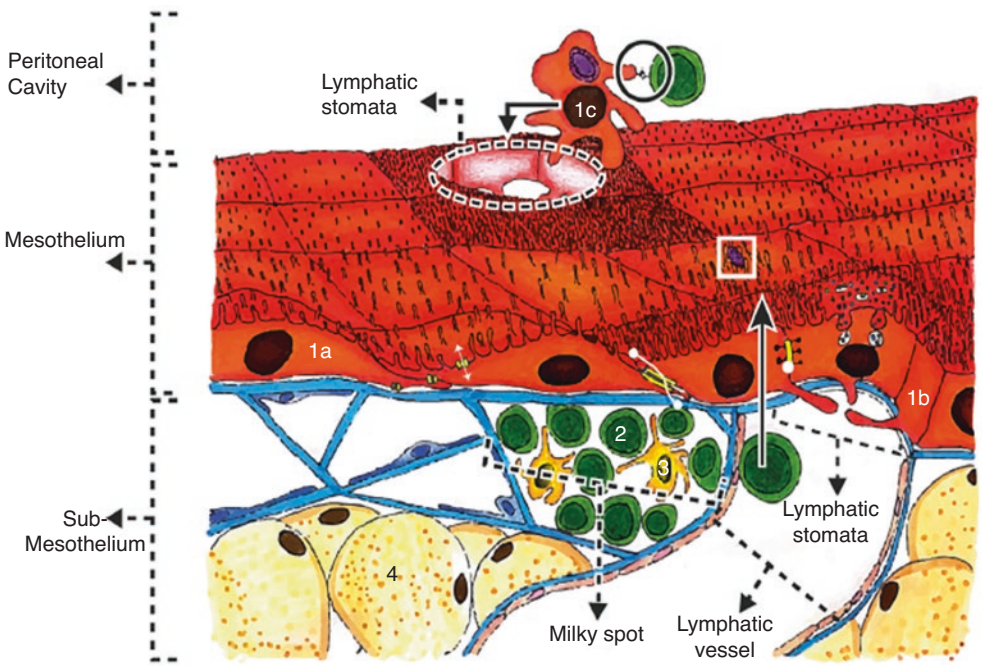


Fig. 3 A schematic representation of the peritoneum with mesothelial organization and functions. The mesothelium is composed of flat mesothelial cells (1a), and cuboidal mesothelial cells (1b). Water transport (two headed white arrow) occurs through aquaporins, while zonula adherens (two headed dot arrow) and tight junctions (white dot) give support and selective barrier properties. Mesothelial cell can also trap pathogens (white square), detach (1c), phagocyte pathogens and present antigen (black circle) for immune induction. The sub-mesothelium contains the basal membrane, the connective tissue, adipocytes (4) and the milky spots were mainly lymphocytes (2) and macrophages are found (3). Reproduced from [38]

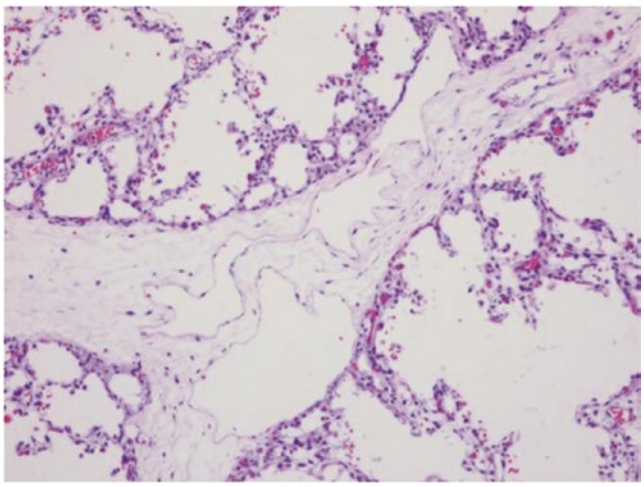


Fig. 4 Photomicrograph of normal visceral peritoneum

Classification and Aetiology of EPS

Encapsulating Peritoneal Sclerosis is currently considered synonymous with the condition which is seen as a long term morbidity of peritoneal dialysis first described by Gandhi in 1980 [42]. However there are a variety of peritoneal sclerosing conditions described unrelated to peritoneal dialysis but associated with specific other pathology. Owtschinnikow described a case of *peritonitis chronica fibrosa incapsulata* as early as 1907 [43]. The abdominal cocoon has been described as a specific entity, unrelated to renal failure or other causes. This presentation has mainly been described in China, India and the African continent with sporadic cases in the temperate regions. Various infective conditions including abdominal tuberculosis has also been described presenting with cocooning of the bowel as a clinical manifestation.

Various descriptive terms have been used to describe the abdominal presentation of these different entities, including sclerosing peritonitis [44], sclerosing obstructive peritonitis [45], sclerosing encapsulating peritonitis [46, 47] and progressive calcifying peritonitis [48]. While the combination of terms are varied, they all fundamentally describe a pathologic process, which is, a sclerosing and fibrosing inflammatory condition, which encapsulates and restricts the gut, leading to bowel obstruction.

Taking into account the incidence, clinical presentations, associations with different aetiology and the clinical and pathologic mechanisms, of the different types of peritoneal sclerotic and encapsulating conditions, it can be broadly classified into three main groups. (a) EPS secondary to peritoneal dialysis, (b) EPS as a consequence of other pathology, unrelated to peritoneal dialysis, and the specific entity (c) Primary encapsulating peritoneal sclerosis. While it can be classified clearly on the basis of etiopathology, it may be difficult to accurately classify it prior to diagnosis [49].

After its initial description in association with peritoneal dialysis by Gandhi [42], the condition has in the last four decades, become recognised as a definite entity which is an uncommon but potentially fatal complication of peritoneal dialysis. EPS associated with long term PD is potentially the most significant of these encapsulating conditions as it can be associated with significant morbidity and mortality. It is a relatively uncommon complication of PD which varies between centres, countries and over time periods. The prevalence of EPS varies from 0.4% to 8.9%, its incidence rate between 0.7 and 13.6 per 1000 patient-years. This observed variability may be multifactorial, including genetic predisposition, significant variation in practice, diagnosis, treatment and follow up of patients [50].

The Pathophysiology of Development of EPS

Due to the large number of patients on peritoneal dialysis globally and the relatively increased numbers of PD related EPS compared to the other secondary and primary EPS, the pathophysiology of this condition has been most studied.

It is now well understood that in the vast majority of cases, development of EPS requires a predisposing factor and also inciting factors. There is not much literature on genetic predisposition; however extrapolating from other genetic fibrosing conditions, there is a strong likelihood there will be a genetic predisposition in association, with long term PD. While peritoneal dialysis is considered more physiological than haemodialysis, the peritoneal dialysis solutions are hyperosmolar are have relative degrees of bioincompatibility, which causes changes to the peritoneal membrane it is in contact with. Factors which cause the bioincompatibility and peritoneal inflammatory reactions are the glucose degradation products (GDPs) after heat sterilisation, the lactate content and the low pH. The pathophysiologic process caused by these factors is similar to a sterile chronic inflammatory process or a chemical burn. It causes denudation of the peritoneal mesothelial cells, epithelial to mesenchymal transdifferentiation, and cytokine release of proinflammatory, proangiogenic cytokines, namely TGFbeta 1, IL-6, CCN2 and VEGEF (Figs. 5 and 6).

Although several precipitating factors have been described for the development of EPS, the main factor appears to be the length of peritoneal dialysis [53] and the recurrent episodes of infective peritonitis. These processes lead to the continued peritoneal inflammatory changes and a cytokine cascade and in genetically susceptible individuals, progression to clinical manifestation as EPS.

The organisms grown in infected peritoneal fluid in patients who go on to develop EPS are mainly Staphylococcus aureus, Propionibacterium acnes [54], Pseudomonas species or Fungal Peritonitis.

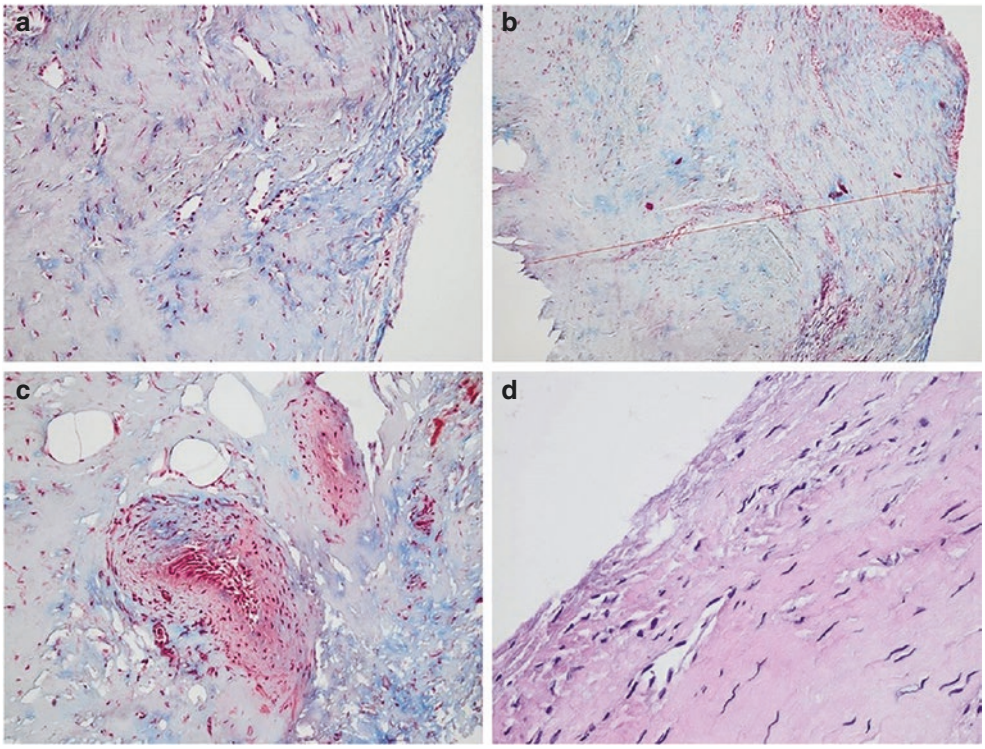


Fig. 5 Peritoneal histological examination: (**a**, **b**) the fibrous components of recent deposition, still rich in mucopolysaccharides, is in a pale color, while the more ancient fibrotic component, consisting almost exclusively of collagen, is highlighted in deeper blue. This staining highlights a recent beginning of the fibrotic process: blue is still poorly represented compared to the pale colour. The thickness of the peritoneal membrane is increased (638 μm). (**c**) Also in perivascular areas, the fibrosis spreads from the submesothelial layer towards the inside. (**d**) Marked thinning of the mesothelial layer. (Adapted from [51])

EPS has been described sporadically after organ transplantation. Lee et al. have described two cases after liver transplantation treated with a combination of surgery, steroids tamoxifen and mTOR inhibitor [55].

It has also been described as a rare complication of intestinal transplantation. In the case described, after confirmatory surgery, the patient was commenced on Sirolimus, and increased steroids and tacrolimus. There was complete resolution of the obstructive symptoms with recovery of intestinal transit [56]. EPS presenting after kidney transplantation is quite well described.

While elements of the predisposing and inciting factors play a part in the other secondary and potentially primary peritonitis, there are other interlinked disease specific factors in addition which will be briefly touched upon.

Secondary Peritoneal Sclerosing Conditions Not Related to Peritoneal Dialysis

Secondary Peritoneal Sclerotic conditions unrelated to peritoneal dialysis encompasses a very large and disparate group of conditions (Table 2). They span a spectrum of aetiopathology with, the clinical manifestations caused by, both the primary disease and the superimposed effects of peritoneal sclerosis with or without membrane formation and/or encapsulation.

The earliest cases of encapsulation were related to foreign material introduced during surgical procedures. The use of Talc, has been known to cause fibrosis [57] Talc powder was used as a lubricant for surgical gloves in the past, before its detrimental effects were identified. Silica is a component of talc, and causes fibrosis, with a characteristic and diagnostic histologic feature, the Maltese cross. EPS has been reported in a drug abuser where it is postulated that silica got into the abdomen through abdominal injections [58]. Povidone iodine used for peritoneal lavage after surgical procedures has also been reported to cause EPS [59]. Dacron fibres as a cause in an individual has been reported, however this patient was on peritoneal dialysis, and the EPS was precipitated after change of the dialysis catheter [60].

Other than externally introduced material, body fluids could precipitate EPS. Encapsulation after abdominal trauma has been described [61]. It is hypothesized that subclinical peritonitis may be the underlying cause in this case. Similarly EPS secondary to rupture of a Dermoid cyst has been reported where the authors postulate the mechanism to be a chemical peritonitis from the cyst contents [62].

Sigaroudinia et al. describe EPS as a complication of long term ventriculo-peritoneal shunts two children who required surgical enterolysis. Both of them presented with acute intestinal obstruction. The CSF was sterile in both these patients. No specific mechanism is postulated other than chronic irritation [63].

EPS has also been described as part of manifestation of systemic inflammatory diseases. It is described along with recurrent ascites in SLE. The mechanism may be related to the inflammation of serosal membranes, including perito-

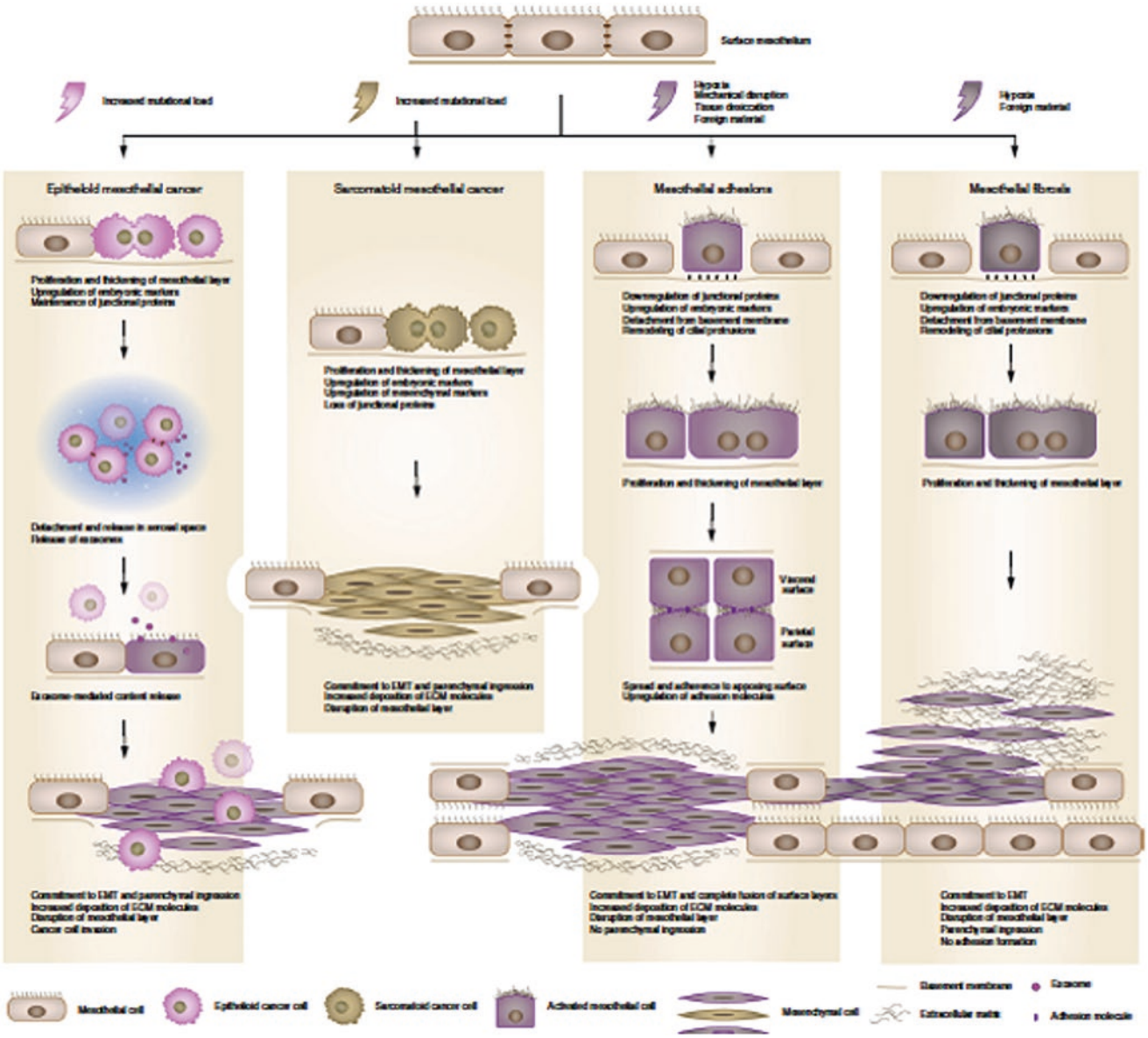


Fig. 6 Schematic representation of a cross section of the peritoneum showing mesothelial-to-mesenchymal transition (MMT) as a consequence of cancer or, for example long-term peritoneal dialysis. Reproduced from Tim Koopmans, Yuval Rinkevich: Mesothelial to mesenchyme transition as a major developmental and pathological player in trunk organs and their cavities [52]

neum, pericardium and pleura associated with SLE. On the background of a genetic predisposition, encapsulation and ascites develops [64, 65]. A similar mechanism may occur in Familial Mediterranean Fever which is associated with polyserositis [66].

Another group of diseases which are associated with EPS are the ovarian tumours. Leutenising thecomas are most closely associated with the condition. The link was first described by Clement in 1994, in six patients, where leutenizing thecomas were associated with peritoneal sclerosis [67]. The thickened peritoneum was made up of a proliferation of fibroblasts and myofibroblasts separated by collagen, fibrin and chronic inflammatory cells. The causative relation was thought to be enigmatic. Altman et al. have reviewed the linkage and identified 43 cases, and on immunohistochemistry, vimentin+/keratin+/CD34+ was found [68].

One of the first drug related causes was reported in 1975 in association with practolol for angina [69]. The patient required surgery for obstruction, where there was fibrinous adhesions and cocooning of gut which required excision and enterolysis. Subsequently other drugs in the beta blocker class have also been found to cause EPS including Timolol. Antiepileptic drugs like phenytoin have also been implicated with the authors postulating that like gingival hyperplasia, the mechanism might be increased collagen and glycosaminoglycans and peritoneal inflammations with

Table 2 Classification of encapsulating peritoneal sclerosis

A: EPS secondary to peritoneal dialysis
B: EPS secondary to other well-defined pathology
Drug related
Practolol
Methotrexate
Antiepileptic drugs
Intraperitoneal chemotherapy
Infections
Tuberculosis
Non-tuberculous mycobacteria
Bacterial peritonitis
Cytomegalovirus infections
Fungal infections
Parasitic infections
Neoplasms
Leutenising thecomas
Leutinising granulosa cell tumours
Abdominal trauma
Foreign bodies
Talcum powder
Asbestos
Silica
Endometriosis
Dermoid cyst rupture
Systemic inflammatory conditions
Sarcoidosis
Systemic lupus erythematosus
Familial Mediterranean fever
C: Primary EPS (the abdominal cocoon)

adhesions and cocooning [70]. Methotrexate has also been reported as an aetiological factor [71–73]. EPS associated with direct intraperitoneal chemotherapy has been reported [74, 75].

Intraabdominal tuberculosis can also present with the granulomatous tissue encasing the bowel and presenting as an abdominal cocoon. It is important that a preoperative diagnosis is made as anti-tuberculous treatment may resolve the problem. However if it presents as bowel obstruction not responding to treatment or an acute surgical emergency, surgery has to be carried out and histological confirmation obtained [76–78].

Mycobacterium fortuitum, an atypical mycobacterium has been reported, however in association with peritoneal dialysis [79]. There are several case reports of EPS associated with fungal infections,

Primary EPS

Foo et al. in 1978 published on series of cases in young girls from Singapore where the gut was encased in a membrane causing obstruction [80]. The condition was termed the abdominal cocoon. Histologically the membrane was made of thickened collagenized fibrous tissue with mild vascularization. Subsequently there have been several reports of this condition mainly from the tropics and subtropical regions. The largest number of publications on this condition comes from China, India, Turkey and Nigeria. However there have been cases also described in temperate zones [81, 82].

No underlying cause can be ascertained in primary encapsulating peritoneal sclerosis and hence the name and the differentiation from the secondary group of EPS. There have been several hypotheses, on the aetio-pathologic processes of development of this condition, including retrograde menstruation, superadded viral infection, retrograde peritonitis via the fallopian tubes and immunological reasons [83]. The condition is however also seen in men, premenopausal women and children. It is difficult to diagnose clinically preoperatively, but a CT scan can make the diagnosis. Careful dissection and excision of the thick sac with release of the small intestine leads to complete recovery in the vast majority of cases [84].

Diagnosis of EPS

The diagnosis of EPS requires knowledge of the condition and index of suspicion in patients presenting under the different contexts referred in the classification above. It should be considered in the differential diagnosis of an individual on long term peritoneal dialysis who presents with abdominal symptoms with progressive decline in nutritional status and raised inflammatory markers. The majority of patients on long term peritoneal dialysis do not develop EPS. However EPS should be considered and ruled out in any patient who has had peritoneal dialysis for a number of years (over 5), and especially so in someone with a history of multiple episodes of peritonitis.

In susceptible patients it may present soon after a transferring from peritoneal dialysis to haemodialysis, or after transplantation in someone who has been on long term peritoneal dialysis. The exact mechanism of how EPS is precipitated after this modality change is unknown.

It should also be considered in patients who have had previously had peritoneal dialysis who present with recurrent episodes of unexplained ascites, especially after transplantation or after conversion to HD.

In a significant number of patients, the diagnosis is made late after investigations for other pathology have drawn a blank. If the condition is not considered early, patients often decompensate nutritionally while being investigated for other potential pathology and in that period continue to decompensate nutritionally. In parallel with these changes, if the individual is still on peritoneal dialysis reduction in ultrafiltration will be noted along with a high transporter status. The deterioration is hastened by the underlying inflamma-

tory process in the peritoneal cavity driven mainly by the thickened and inflamed membrane.

In the early stages patients may present with vague abdominal symptoms, and then develop refractory anaemia which does not respond to iron supplementation or erythropoietin. This is also related to the chronic inflammatory process, from the thickened membrane and also pockets of loculated peritoneal collections. These collections usually contain debris, clots and fibrinous material and organisms. The CRP will be raised right from the outset and along with disease progression and there will be a downward trend in albumin levels (Table 3).

In the non PD group of EPS, the diagnosis may be even more difficult, and diagnosis depends on knowledge of association of EPS with that condition, an index of suspicion and imaging.

A significant number are unfortunately diagnosed at surgical exploration. There can be rare and unexpected presentations [85, 86]. There are also instances, where EPS can present without any pre-existing symptoms [87].

Table 3 Symptoms and clinical features of EPS

History
Peritoneal dialysis, with episodes of peritonitis
Increased risk if peritoneal dialysis over 5 years
Change of modality of dialysis within last 6 months or transplantation
Symptoms of fullness, discomfort
Abdominal distension or bloating
Fullness, early satiety, vomiting
Significant loss of weight
In late cases gross distension, obstruction
May also present acutely with obstruction, peritonitis or hemoperitoneum
Clinical features
Anaemia
Weight loss and cachexia in advanced cases
Abdominal distension
Fluid collection as ascites or loculated abdominal fluid
Palpable abdominal mass from the cocoon
Investigations
Anaemia
Raised CRP
Leucocytosis
Hypoalbuminemia
Imaging (X ray/US Scan/CT/MRI)
Thickened peritoneum
Ascites
Mesenteric retraction
Obstructive features with thickened bowel
Calcification

The above features are primarily consistent with EPS associated with peritoneal dialysis. In primary EPS and other forms of secondary EPS, the diagnosis, is one of exclusion mainly of other causes, and considering individual clinical presentations

Diagnostic Tests and Pathway for Suspected EPS

There are no specific single blood tests that point to EPS, however the combination of refractory anaemia, often a leucocytosis, hypoalbuminemia and a persistently raised CRP in the context of a patient receiving of having received PD is suggestive.

In individuals who develop post-transplant EPS, there may be derangement of transplant kidney function from a combination of inflammation, infection and dehydration from intraperitoneal fluid collections.

In the other secondary causes of EPS, the relevant disease specific investigation screens along with abdominal imaging may help make the diagnosis.

Imaging in EPS

A plain X-ray may show areas of peritoneal calcification, especially in long standing cases. Characteristic calcification on the bowel surface and the peritoneum is an important diagnostic feature which could alert the clinician to the diagnosis. An erect abdominal film may show some evidence of early obstructive features, such as air fluid levels or evidence of frank obstruction in an acute presentation. Other than these features which may enhance diagnostic suspicion of EPS, in the modern era, the role of the plain abdominal X-ray in these conditions may be redundant.

Abdominal Ultrasound is helpful in that it may show ascites and peritoneal fluid collections and in classic cases, can demonstrate the thickened membrane cocooning the gut, and dilated loops of obstructed gut (Fig. 7). For these findings to be diagnostic, they should be considered along with the clinical context. Abdominal ultrasonography is important in guiding paracentesis in some patients who present with recurrent accumulation of ascites. It is also important in the diagnosis of postoperative intraabdominal collections after enterolysis and peritonectomy.

The CT scan is the modality of choice in the diagnosis of EPS. Diagnostic features of a CT scan are peritoneal thickening, abdominal tethering, dilated gut, fluid accumulation as loculations of fluid or frank ascites, and areas of localised or generalised calcification of the peritoneum (Fig. 8). The CT findings depend on the stage and severity of the disease. In the early stage, the thickening of the peritoneum may be subtle, however, there may be suggestive features of gut tethering with some localised dilatation of loops of bowel [88, 89].

MRI Scans are also as valuable or sometimes provide more definitive detail of the pathology [90]. However either the CT scan or the MRI scan will provide diagnostic radiologic features that could lead to a confirmatory diagnosis of

EPS (Fig. 9). Cine MRI has been used as an experimental modality [91], where pathologic features of the encapsulation along with the restrictive effects of the cocoon can be demonstrated.

Vadi SK et al. have reported the use of ^{18}F-FDG PET-CT as a modality in the diagnosis of the abdominal cocoon associated with tuberculosis (Fig. 10) [92].

Laparoscopy

Once a diagnosis of EPS is considered, it can be arrived at by correlating the clinical history, clinical examination, blood tests and the radiologic imaging. However, there are situations when symptoms will still remain unexplained and obscure but point to an intraabdominal source. In these situations, laparoscopy may be useful for visualising the peritoneal cavity for definitive diagnosis, ruling out pathology and also for obtaining diagnostic samples.

The critical points in laparoscopy are to ensure that there is no perforation due to the cocooning (Fig. 11). An important decision when carrying out laparoscopy for diagnosing EPS, is planning intervention. If EPS is definitely found on laparoscopy, it may be best for surgical intervention to be planned at a later date.

Histologic Features of EPS

The diagnosis of EPS is a clinical diagnosis and not histological. Histology of the peritoneal membrane in a patient with EPS may show characteristic features that confirm the clinical diagnosis. It is also important in ruling out, secondary causes of peritoneal sclerosis or pathology including tuberculosis or malignancies. Histologic changes reflect the effect on the peritoneum caused by the hyperosmolar dialysis fluid and is seen in both the parietal and visceral peritoneum. The peritoneal membrane thickens and scleroses in long standing peritoneal dialysis, along with mesothelial

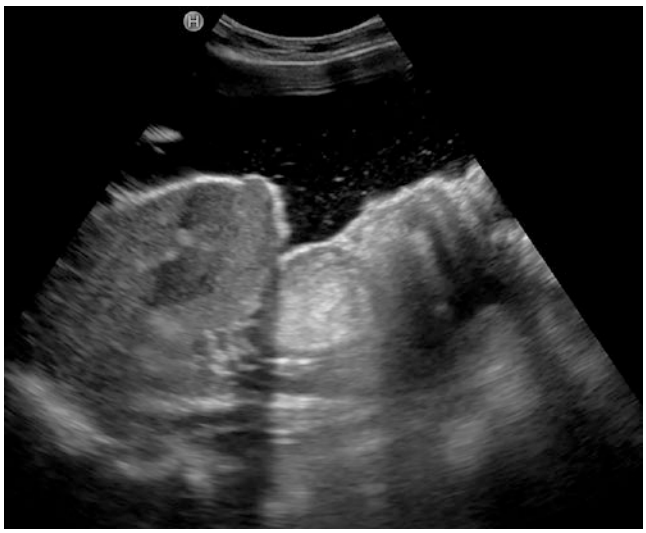


Fig. 7 A single static ultrasound image showing the liver with calcification on the surface, ascites and cocooned gut with calcification on the surface

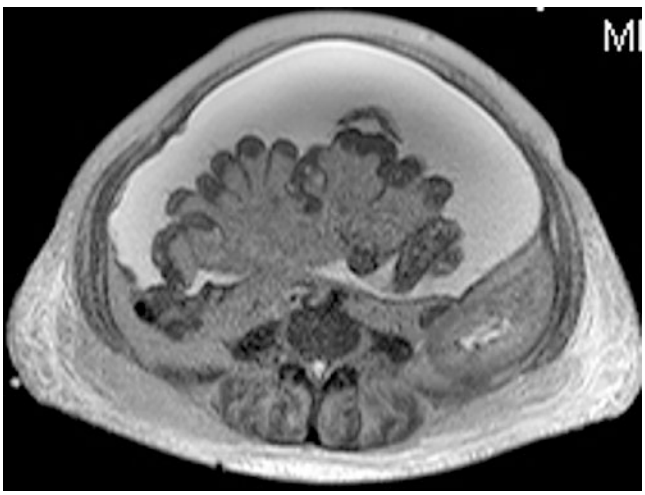


Fig. 9 An MRI scan showing the same features in the same patient, with subtle differences. The calcification is not as prominent, and the thickening of the peritoneum is not as evident in MRI scan compared to the CT scan

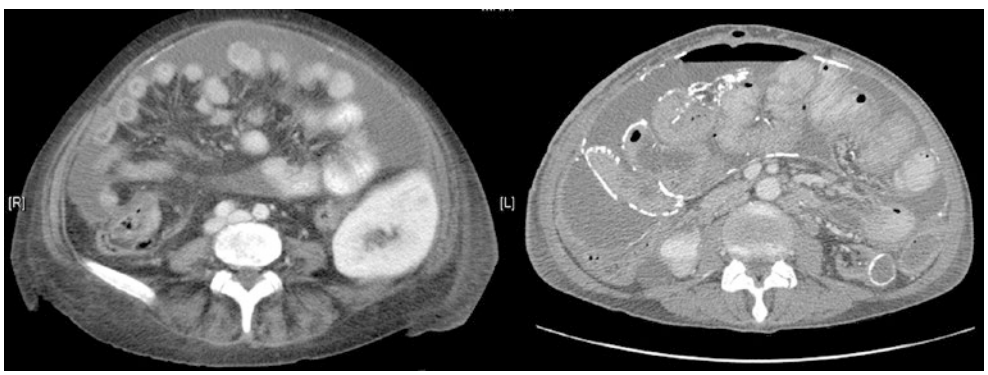


Fig. 8 CT scans demonstrating free fluid, thickening of both parietal and visceral peritoneum with certain areas of calcification, mesenteric retraction and some gut dilatation. The first image is of a patient with post-transplant EPS and there is a good functioning kidney in the left flank

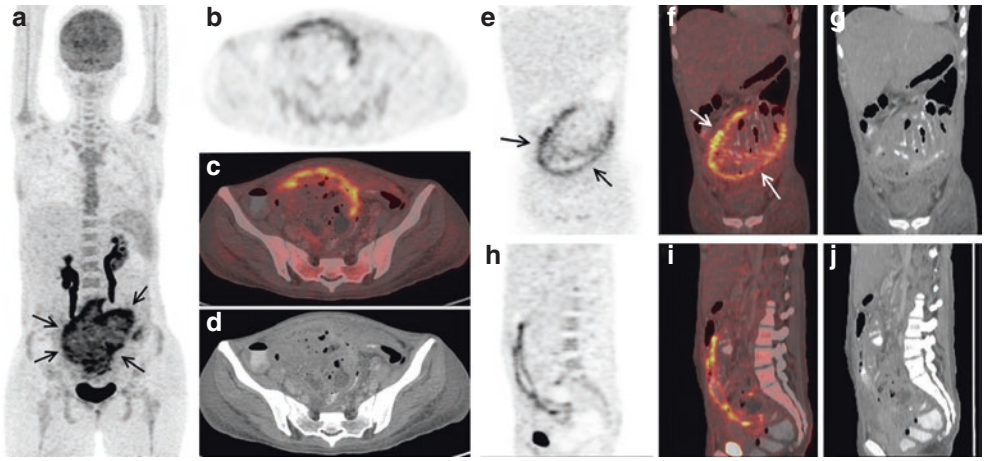


Fig. 10 FDG-avid peritoneal thickening encapsulating around the clumped jejunal and ileal loops forming a tracer-avid "cocoon" in the abdomen as shown in the MIP (**a**; arrows), axial PET (**b**), fused PET/CT (**c**), axial CT (**d**), and corresponding coronal (**e**, **f**; arrows and **g**) and sagittal (**h**, **i**, and **j**) images, suggesting sclerosing encapsulating peritonitis (SEP)

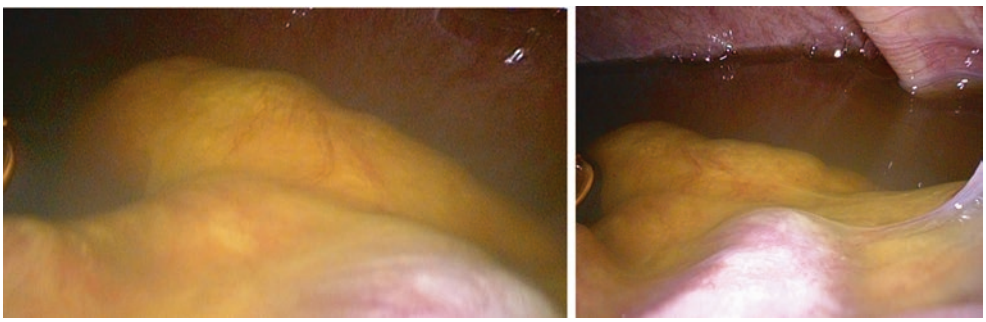


Fig. 11 A laparoscopic image showing early EPS in evolution. The ascitic fluid is turbid and there is encapsulation of the gut with neovascularization of the surface. The membrane can been seen and is thin and flimsy as it is early in its formation. If left undiagnosed or untreated, it will develop into the thick constricting collagenous membrane seen in advanced disease and will eventually calcify

denudation. Below the mesothelial layer, the compact zone thickens and is formed of myofibroblasts and fibrous collagen [93]. The vasculature in this layer undergoes changes, with medial sclerosis and hyalinization, along with neoangiogenesis [94]. Honda et al. have also described fibrin deposition, increase in the size of the fibroblasts, capillary angiogenesis and mononuclear cell infiltration were more common features of EPS rather than simple sclerosis [95]. Advanced glycosylation end-products are found in the mesothelial and sub-mesothelial layer of PD patients [96, 97].

Additional histological findings identified by different investigators include, positive immuno-histochemical staining for podoplanin [98] and upregulation of vascular endothelial growth factor (VGEF) and downregulation of mast cells [99, 100]. All these findings however are not specifically related to EPS, and could be seen in the different peritoneal fibrosing conditions.

Histology of Non-renal EPS

Histologic features of secondary encapsulating peritoneal sclerosis or peritoneal fibrosing conditions are more specific and often diagnostic when compared to EPS associated with peritoneal dialysis. Examples are peritoneal tuberculosis where typical granulomatous inflammation is seen with or without necrosis and acid fast bacilli.

In malignant encapsulation, the histologic features will depend on the specific malignancy which is causing the pathologic manifestation.

In the primary or idiopathic cases of EPS, histologically, the peritoneum will show a proliferation of fibro-connective tissue, inflammatory infiltrates, and dilated lymphatics. There will be no evidence of granulomas, giant cells or birefringent material.

Treatment of EPS

As soon as a diagnosis of EPS is made in PD related cases, it is imperative that the patient discontinues peritoneal dialysis and is established on haemodialysis. A strategy that has been tried in preventing the development of EPS is regular peritoneal lavages after discontinuation of PD. Regular lavage has been shown to help mesothelial cell repair [101].

While this is a strategy that can be attempted in the very early stages without mechanical obstruction, nutritional deficiency or significantly raised inflammatory markers, it

should perhaps be carried out in conjunction with additional medical therapy. There is no robust scientific basis.

In the group of patients presenting mainly with significant and recurrent ascites, paracentesis will be required for relief of discomfort. More than one attempt at paracentesis will be required as the peritoneal fluid may continue to reaccumulate. Depending on the individual clinical context, concomitant medical therapy may be required. In these clinical situations where there is no overt mechanical obstruction, a decision on surgical intervention, may be difficult to justify. However if there is recurrent, re-accumulation of fluid, there may be justification in surgery with a view to a peritonectomy of the thickened membrane. The membrane in these situations is often a strong impermeable fibrocollagenous membrane overboth the parietal and visceral peritoneum which prevents the reabsorption of peritoneal fluid. Once stripped off, and peritoneum excised, there is the establishment of fresh peritoneum which aids in absorption.

Medical Therapy for EPS

Various medical forms of therapy have been described for EPS, however most medical interventions are anecdotal without any specific clinical trials to determine the effectiveness of therapy and outcomes. It will also be very difficult to evaluate the impact of the medical therapy on the natural progression of EPS.

Steroids

Corticosteroids have been used as medical therapy by different teams at different points in the disease process. The rationale for steroid use is that it inhibits collagen synthesis and maturation by suppressing the inflammatory process. The beneficial effects of estradiol propionate was experimentally demonstrated in nonuremic Wistar Albino rats [102]. Kuriyama has reported good outcomes in all patients treated with steroids compared to poor outcomes in those not on steroids [103]. Several other groups have also reported on the beneficial effects of steroids in EPS [104, 105].

Tamoxifen

With a solitary case report in 1999, Tamoxifen began to be used as medical therapy largely because there was no well-defined consensus strategy for therapy of EPS once diagnose. The rationale of the authors was that Tamoxifen, a selective estrogen receptor modulator interferes with TGF beta 1, a probiotic cytokine [106]. Transforming growth factor beta 1 (TGF B1) has a stimulatory effect on matrix metalloproteins (MMP 2 and 9). MMP9 degrades Type IV and denatured collagens, TGF beta 1 production, which is stimulated by tamoxifen, might favour mesothelial healing by facilitating the removal of denatured collagen. It has been successfully used in the treatment of retroperitoneal fibrosis [107, 108] and long term therapy for idiopathic RPF has been found to be effective and safe [109].

Immunosuppression

Immunosuppressive agents other than steroids have been used to good effect by different teams. Azathioprine in combination with steroids has been shown to be effective [110]. mTOR (Mammalian target of Rapamycin) inhibitors, including Sirolimus, have been used by several groups especially in patients after transplantation, including liver transplantation with response [111, 112].

Novel Agents

Danford et al. hypothesise that while mechanical obstruction is the main underlying factor, dysmotility may play a role through the disruption of the myenteric plexus by fibrosis and increased endogenous opioids from activated lymphocytes inhibiting both propulsive motor and secretory activity in the gut [113]. Methylnaltrexone to combat inflammation associated dysmotility has been described in anti-Hu associated intestinal pseudo-obstruction [114]. Altman et al. have suggested targeting vimentin+/keratin+/CD34+ tissue in patients with leutenizing thecomas and sclerosing peritonitis [68]. ACE inhibitors may make peritoneal fibrosis progress more slowly [115]. Animal studies have found hepatocyte growth factor [116], TNP-470 [117] and antisense oligonucleotides to reduce peritoneal fibrosis [118].

Caveats in Medically Treating EPS

While medical therapy may be attractive for both the patient and the treating clinician from the point of view of avoiding a major surgical procedure with associated morbidity and mortality, it is based on anecdotal reports and small case series. There is always the potential risk that the diagnosis may be incorrect. Steroids may mask inflammation and cause continued progression of disease. Defining length of medical therapy may be difficult and disease progression during medical therapy may cause acute obstructive, infective, and haemorrhagic complications including perforations. This may require emergency surgical intervention. Surgical intervention in acute situations in patients on steroids and mTor agents can cause significant unwanted morbidity. This is due to the friability of tissue and difficult healing, increasing the overall chances of morbidity and mortality.

Surgery for EPS

There is universal consensus that in patients with encapsulating sclerosis presenting with intestinal obstruction, surgery is the most effective treatment. The underlying problem in these patients, is mechanical bowel obstruction caused by a combination of the thickened inflamed peritoneum, the fibrocollagenous membrane and adhesions. Bowel is in most instances encased in this pathologic tissue.

The principles of surgery are the very careful release of the obstructing, sclerotic and encapsulating membrane and releasing, gut so that it remains free in the peritoneal cavity, with the reestablishment of peristalsis. Surgery requires meticulous attention to detail and technique and dissection, and ensuring that in the process of releasing obstructed gut, a perforation is not made or there is bleeding from vascular tissues or vascular structures. One of the main reasons for reported poor outcomes in EPS in international literature and the high mortality is the fact that if surgical teams do not have experience with this entity, decision making and judgement during acute presentations proves extremely difficult. With acute presentations in patients especially in renal failure and on dialysis, who have decompensated nutritionally over long periods of time, managing a hostile encapsulated abdomen can prove extremely challenging. Hence best outcomes are achieved by teams who have experience in the management of the condition.

There are only a handful of centres in the world which have significant experience in the surgical management of the condition. Clinical outcomes from these centres have improved. Various different terms are used for surgery, including peritonectomy and enterolysis (PEEL) procedure [119]. Another limited procedure which has been described is Capsulotomy [120].

Preoperative Preparation and Planning

Once a definitive diagnosis of EPS has been made, therapy has to be tailored to the individual patient. A risk benefit balance decision has to be critically made after, a thorough evaluation of the patient, investigations and imaging. If the CT scans show cocooning of the gut, surgery is indicated as it is highly unlikely that any medical therapy will reverse the gut problems. Surgery is the gold standard treatment for the condition except for the most early of cases. There are numerous individual case reports and small series reports on surgery and outcomes. A small number of international centres have consolidated experience in surgical management [119, 121]. Surgical intervention is planned depending on the overall clinical state.

All patients should have a full cardiovascular assessment for anaesthesia, including an echocardiogram and if possible a cardiopulmonary exercise test. Respiratory physiotherapy prior to surgery will improve operative outcomes. Patients should be managed by experienced anaesthetists, skilled in the anaesthesia for patients with chronic renal failure with significant morbidity.

If patients present as an emergency with evidence of peritonism, where surgery is indicated immediately, it has to be carried out, although the mortality and morbidity associated with emergency surgery in EPS is over 50%. In an elective or semi elective situation, all patients should have a thorough nutritional assessment as a significant percentage of these patients will have evidence of poor nutrition [122]. Anthropometrics, will identify depleted fat and lean body mass which can increase surgical morbidity and mortality [123]. All patients undergoing surgery should have augmented and intensive preoperative nutrition including parenteral nutrition. Parenteral nutrition will in all likelihood need to be continued well into the postoperative phase, as return of gut motility with the ability for oral intake may be prolonged. It is of critical importance that parenteral nutrition be given through a dedicated access line, with all the precautions and care taken to ensure asepsis and sterility. An infected access line could cause significant morbidity and mortality. In a significant majority of these patients, there will need to be alternate access for haemodialysis.

As perioperative fluid management is critical, and inadequate dialysis can lead to fluid retention and increase perioperative morbidity, it is imperative that all patients have optimum haemodialysis prior to surgery, and ideally daily dialysis.

The aims of surgery in EPS are fundamentally to relieve the mechanical gut obstruction which is contributing to the symptoms and malnutrition and also clear as much as possible of the thickened and inflamed membrane which is contributing to the chronic inflammatory process and the anaemia. Both the parietal and visceral peritoneum will be thickened and where there is obstruction, the gut proximal to the obstruction will be thickened (Fig. 12). The surface of the bowel below the membrane will be tanned and of the thickened and encapsulating membrane however has to be balanced on the requirement to relieve intestinal obstruction and the need to avoid iatrogenic gut perforations which can precipitate enteric fistulas and exponentially increase postoperative mortality.

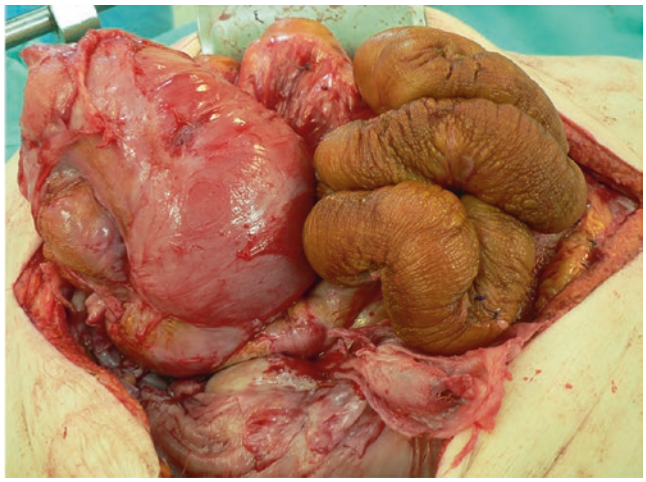


Fig. 12 Dilated proximal gut with released tanned, distal encapsulated segment, during enterolysis

Surgical Technique

Abdominal entry is through a long midline incision, after recent cross sectional CT images have been reviewed. It is important to first enter an area of the peritoneal cavity where gut is not adherent to the anterior abdominal wall, to avoid a perforation. If a perforation occurs during surgery, primary closure almost invariably fails due to the thickened and diseased tissue, leading to an enteric fistula and significantly increased mortality. The technique used in the author's centre is to develop a plane outside the abdominal cocoon, bilaterally. Once that plane has been developed, the cocoon is entered in an area where there is fluid (Fig. 13). Progress of surgery is dictated by findings on abdominal entry. Once the peritoneal cavity is entered in a suitable area, all fluid and debris is aspirated, after samples are taken for culture and sensitivity, biochemistry and for acid fast bacilli.

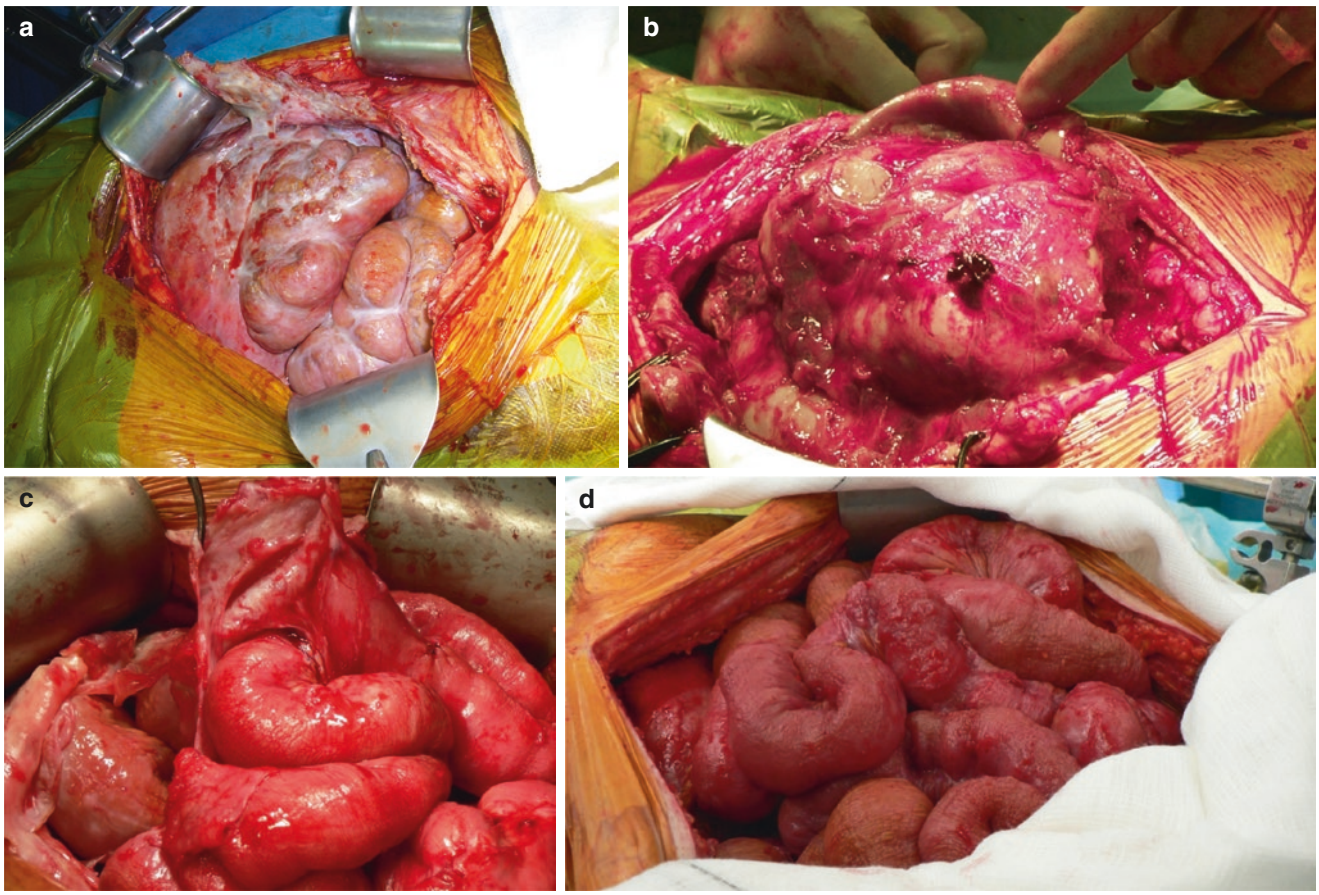


Fig. 13 The encapsulated gut with dense sclerotic adhesions between loops of bowel and also the encapsulated gut and the liver (**a** on entry outside the cocooned bowel, **b** after some dissection, **c** releasing fibrotic membrane from gut and **d** after completed enterolysis). The extremely thickened and almost calcific parietal peritoneum can also be seen and adhesions also between the sclerotic mass and the abdominal wall

The peritoneal cavity is then inspected and the exact degree of the encapsulation understood. Dissection is then commenced in an area and then meticulously extended, releasing loops of bowel, which are clumped together by the membrane. The membrane is adherent to the gut surface, by a firm interface. With careful blunt and sharp dissection the membrane can be dissected off, however it is critical that there are no perforations made. If perforations are made, the propensity for post-operative leaks and fistulation, increases significantly. A decision is made about simple closure or a stoma formation. Dissection is then carried out, releasing the entire gut, right from the DJ flexure till the ileo-caecal junction. The terminal ileum is one of the most important areas as it is the most common area affected by the sclerotic membrane.

Localised EPS

While EPS is in most situations generalised, there are situations where cocooning can be entirely localises to a segment of gut, especially the terminal ileal region [124].

The Management of Advanced Cases Where Enterolysis and Peritonectomy Is Not Possible

Cases may present acutely from time to time where at surgery the abdomen is too rigidly encased in sclerotic tissue, or badly calcified, where enterolysis and peritonectomy is technically impossible. Attempting lysis in these situations may cause perforations, bowel fistulae and mortality. In these situations, the most appropriate course of action would be to close the abdomen and considering long term parenteral nutrition. However, there are several case reports in literature where individual cases have been managed with different techniques including a loop jejunostomy in a case of recurrent EPS where the original presentation was a uretero-ileal fistula [125]. The same group has also described placement of a percutaneous gastrostomy tube with jejunal extension, to drain gastric and proximal gut secretions while providing total parenteral nutrition [126]. Combined bowel and kidney transplantation has also been reported [127]. It demonstrates the feasibility of the technique, and where renal failure too is addressed by the transplanted kidney.

Recurrent EPS

In spite of the best surgical treatment, there may be a significant risk of recurrence of up to 25% [128]. The Japanese group which has one of the largest international experiences with the condition, have utilised different techniques, including fixing the bowel with a long intestinal tube, to maintain patency, and the use of the Noble Plication technique [129].

The management of recurrent disease is exactly the same with repeat surgery and further enterolysis and peritonectomy.

Encapsulating Peritoneal Sclerosis in Children

EPS has been described in children who have had long term PD. The prevalence of EPS in European children on PD is comparable with that of the adult patients. A high index of suspicion is required for diagnosis in children with longer dialysis duration, peritonitis rate and UF failure [130, 131].

Dietary Therapy (to Avoid Obstructive Symptoms with Adhesions and EPS)

Occasionally a completely liquid diet is required to avoid obstructive type pains in patients with adhesions or EPS. Review by an experienced dietitian should be provided for all patients with chronic symptoms.

Definitions

Dietary fibre has been defined as carbohydrate polymers with ten or more monomeric units, which are not hydrolysed by the endogenous enzymes in the small intestine of humans and belong to the following categories [132]:

- Edible carbohydrate polymers naturally occurring in the food as consumed
- Carbohydrate polymers, which have been obtained from food raw material by physical, enzymatic or chemical means and which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities
- Synthetic carbohydrate polymers which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities

Plants often contain a mixture of soluble and insoluble fibre. Soluble fibre increases the viscosity of bowel contents, slowing down digestion and the absorption of nutrients. Insoluble fibre has a high water binding capacity which results in softer and bulkier bowel contents to aid the acceptable functioning of the gut. Cereal fibre is reported to have the greatest bulking effect [133]. It is these effects which has led to the use of low fibre diets in the treatment of adhesions and obstruction.

In 2014 the British Dietetic Association published a systematic review on the management of Crohn's disease. This review was unable to identify any trials to recommend the use of low fibre diets in structuring disease to minimise the risk of bowel obstruction or reduce symptoms [134]. The opinion of the group, which consisted of expert Dietitians, was that fibre should be avoided in stricturing Crohn's disease to reduce the possibility of a mechanical obstruction. In addition, a low fibre diet may be helpful in reducing peristomal pain from excess gas production. The lack of scientific evidence to support the use of a low fibre diet does not negate their use in clinical practice as it is difficult, from an ethical perspective, to conduct clinical trials where dietary fibre could result in a mechanical obstruction. The BOUNCED feasibility study at the Royal Surrey County Hospital NHS Foundation Trust is aiming to investigate the use of dietary manipulation in bowel obstruction (see below). It is envisaged the results will be influential in establishing a consensus and provide the standard for dietary guidelines for bowel obstruction.

Low Fibre

There are no clear definitions in the literature on what constitutes a low fibre diet. One study investigating the effect of a low fibre diet in patients with IBS aimed for 10 g of fibre per day [135]. Another study used <10 g of fibre as bowel preparation 1 week pre surgery [136] and therefore not applicable in the long term setting of bowel obstruction.

Low Residue

To date there are no agreed definitions of what constitutes residue and in 2012 the American Academy of Nutrition and Dietetics removed the term "low residue diet" from the Nutrition Care Manual [137]. This is because the amount of residue produced during the passage of food through the gut cannot be quantified as includes undigested food, microorganisms, gastrointestinal secretions and cells from the intestine. Therefore, for the purposes of this chapter the term low fibre will be used.

Causes of Bowel Obstruction

There is limited literature describing the dietary intake of patients with bowel obstruction but patients with recurrent bowel obstruction are known to have a reduced quality of life and their condition has an impact on their dietary intake. In a study of 48 patients with recurrent bowel obstruction ranging from two episodes during their life to monthly episodes, 90% of patients reported an impact on their diet [138]. There are many case reports in the literature regarding different types of food causing bowel obstruction in both patients who have had previous abdominal surgery and those with a virgin abdomen (Table 4).

Due to the intermittent nature of bowel obstruction, different levels of restriction may be required depending on symptoms and the degree of obstruction. Radiological images may help ascertain the degree of obstruction and inform the dietary restrictions required. Patients with severe adhesions or strictures may require a liquid diet whereas patients with partial obstruction may be able to manage some fibre containing foods. The BOUNCED study from the Royal Surrey County Hospital NHS Foundation Trust is investigating the use of a 4-step bowel obstruction diet in patients with cancer (step 1 clear fluids, step 2 all thin liquids, step 3 smooth or pureed foods only low fibre, step 4 soft sloppy foods low fibre) [139].

Each patient will have different tolerance levels which may change over time Therefore, it is important that restrictions are reviewed regularly and if possible lifted to allow

Table 4 Foods reported to have caused bowel obstruction

Foods
Fruit
• Cherry tomato
• Dried apricot
• Dried fruit
• Persimmon
• Dates
• Grapes
• Orange pith
• Peach stone
• Plum stone
• Apricot stone
Vegetables
• Artichoke
• Mushrooms
• Shitake mushrooms
• Olives
Nuts
• Brazil
• Chestnut
Seeds
• Prickly pear
• Granadilla
• Medlar
• Sunflower
Other
• Bran
• Oat bran
• Ginger
• Egg yolk
• Rice cakes

Table 5 Principles of a low fibre diet

• Wholemeal bread to white bread
• Brown rice to white rice
• High fibre breakfast cereals to low fibre versions
• Wholewheat pasta to white pasta
• No skins on potatoes
• One portion of fruit a day
• One portion of vegetables a day
• Meat, fish, cheese, eggs, tofu to be recommended to meet protein requirements

as normal a diet as tolerated to minimise symptoms. The principles of a low fibre diet (Table 5) include reducing fibre containing carbohydrates to lower fibre or fibre free alternatives. Fruit and vegetables will need to be peeled, no skins, no pips, no seeds, no pith, no stalks. It is often recommended that only one portion of fruit and one portion of vegetables are taken daily. Beans are high in fibre and therefore should be limited unless vegetarian or vegan when other low fibre protein substitutes should be encouraged (e.g. tofu).

Fluid and Electrolytes

Patients with bowel obstruction are at risk of dehydration and electrolyte abnormalities due to a reduced oral intake and vomiting [140]. Therefore, careful attention should be paid to ensuring patients are meeting fluid and electrolyte requirements as the risk of acute kidney injury (AKI) is high. The National audit of small bowel obstruction in UK found 22% of the patients were admitted with an acute kidney injury [141]. Patients should be educated about the most appropriate fluids (+/− electrolytes) to drink (if not vomiting) to maintain hydration and electrolyte status especially during an acute episode.

Micronutrients

There is no data available on the micronutrient status of patients with bowel obstruction. The low fibre diet which is inherently low in fruits and vegetables, a significant source of micronutrients, means that deficiencies may develop if the obstruction is prolonged and appropriate supplementation will be required. A clinical examination to identify deficiencies should be completed if this is suspected and a complete supplement such as Forceval® or Centrium® recommended. A Registered Dietitian can provide advice on maintaining the nutritional adequacy of a low fibre diet which is why it is important that these patients are referred for advice.

General Advice: Chew and Teeth

Many case studies have also identified the issues of poor dentition and mastication as a contributing cause of bowel obstruction [142–144]. Patients should have any dental issues identified and referral to a dentist if poor dentition is an issue.

Medications

Many medications can cause a reduction in saliva production and therefore a review of medications can be helpful to ensure only essential medication are prescribed. It is known that pharmacobezoars can form from the ingestion of drugs such as cholestyramine and antacids and so their continued use should be evaluated [145]. Furthermore, reports of obstruction resulting from the use of guar gum-containing diet pills have been reported [146] which is why a detail drug history is essential.

Fibre Containing Enteral Nutrition

Whilst there is no evidence to support the view that enteral feeds containing fibre are contraindicated, some authors support this view due to the potential risk of obstruction in those with structuring Crohn's disease [147]. A review of enteral nutrition bezoar formation [148] found 14 cases of obstruction of which at least eight occurred during feeding with a fibre containing enteral formula. Other compounding factors included anatomical changes post operatively, reduced pH, dysmotility, dehydration and medication and therefore the enteral feed may not be the sole causative agent. However, it seems prudent to avoid fibre containing enteral nutrition in cases of severe strictures and adhesions until further research is published.

In conclusion the recommendation to follow a low fibre diet will be determined by the level of the bowel obstruction and likely resolution. Patients will require a Registered Dietitian to provide education and ensure that the diet is nutritionally complete and that reintroduction of fibre containing foods can occur when it is safe to do so.

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