

UK ENCAPSULATING PERITONEAL SCLEROSIS
CLINICAL PRACTICE GUIDELINES
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Produced by UK EPS Clinical Guidelines Group

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INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a serious but uncommon complication of long-term peritoneal dialysis (PD). It is characterised by bowel obstruction and encapsulation due to marked sclerotic thickening of the peritoneal membrane. EPS can result in prolonged debilitating illness and historical series suggest mortality can be high [1-3]. It may be a significant barrier to long-term PD treatment and has a disproportionately negative impact on clinicians' perception of PD as a therapy for ESRD, compared with equally, or more frequent and severe therapy-specific complications in haemodialysis [4,5]. The incidence of EPS varies between 0.5 – 3.0%, increasing with time on PD [1-3,6,7]. Recent data from the Scottish Renal Registry demonstrate a rate of 2.8% in the prevalent PD group, or overall 1.5% in an incident cohort, rising from 0% in first year of PD, to 8.1% (CI 3.6-17.6) at >4-5 years; 8.8% (CI 3.2-23.1) at >5-6 years and 5.0% (CI 1.2-23.8) at >6 years PD

exposure [7]. Greater awareness of the condition may have led to increased diagnosis of milder cases. Mortality was 42% at 1 year after diagnosis, with EPS listed as a contributing cause of death in 14/25 cases [7]. Risk factors for developing EPS are the duration of PD, bacterial peritonitis and perhaps hypertonic glucose dialysate [2,3]. A significant proportion of cases of EPS actually develop after discontinuation of PD [3,7] and transfer to haemodialysis or renal transplantation, with discontinuing PD being a trigger for development of the condition or its clinical manifestations.

The only previous guidelines for management of EPS are from Japan [8], where PD practice differs from UK in that renal transplantation is limited, leading to a greater experience of complications of long-term PD. The greater availability of renal transplantation in UK may lead to differences in the optimum approach to management of these patients.

The recommendations in this guideline have been assessed according to the modified GRADE system. The system was produced by a group of guideline developers and experts in evidence-based medicine. It explicitly describes both the strength of the recommendations and the quality of the underlying evidence, with the aim of maximising applicability to standard clinical practice [9-14]. The system grades level of expert recommendation as “strong” (Grade 1) or “weak” (Grade 2) according to balance of benefits, risk, burden and cost. The quality or level of evidence is assessed as “high” (Grade A), “moderate” (Grade B), “low” (Grade C) or “very low” (D) depending on factors such as study design, directness of evidence and consistency of results. This system has been adopted by the Renal Association Clinical Practice Guidelines Committee and is widely used by a large number of organisations including NICE, SIGN, KDIGO, ERBP, KDOQI, BMJ and WHO [12,15,16]. This guideline has been reviewed and endorsed by the Clinical Affairs Board of the Renal Association.

Grade of Recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A Strong recommendation. High quality evidence.	Benefits clearly outweigh risk and burdens, or vice versa	Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Strong recommendations, can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach.
1B Strong recommendation. Moderate quality evidence.	Benefits clearly outweigh risk and burdens, or vice versa	Evidence from randomized, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise), or very strong evidence of some other research design. Further research may impact on our confidence in the estimate of benefit and risk.	Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C Strong recommendation. Low quality evidence.	Benefits appear to outweigh risk and burdens, or vice versa	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
1D Strong recommendation Very low quality evidence	Benefits appear to outweigh risk and burdens, or vice versa	Evidence limited to case studies	Strong recommendation based mainly on case studies and expert judgement
2A Weak recommendation. High quality evidence.	Benefits closely balanced with risks and burdens	Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B Weak recommendation. Moderate quality evidence.	Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens	Evidence from randomized, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise), or strong evidence of some other research design. Further research may change the estimate of benefit and risk.	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances
2C Weak recommendation. Low quality evidence.	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable
2D Weak recommendation Very low quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens	Evidence limited to case studies	Weak recommendation based mainly on case studies and expert judgement

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1. EPS GUIDELINES 1 (1.1 – 1.2)

Guideline 1.1 – Diagnosis of EPS

Diagnosis of EPS requires the presence of both clinical features of intestinal obstruction/disturbed gastrointestinal function, and bowel encapsulation on radiological imaging (thus differs from simple peritoneal sclerosis of long-term PD) (GRADE 1B).

Audit measure

Proportion of patients given a diagnosis of EPS who fulfil the above diagnostic criteria

Rationale

Diagnosis of EPS is made on the basis of a combination of bowel obstruction and features of encapsulation due to peritoneal fibrosis [1]. It differs from simple peritoneal fibrosis or thickened peritoneal membrane without the presence of obstruction / encapsulation. Symptoms such as anorexia, nausea, vomiting, and weight loss are common [2], and features of gastrointestinal obstruction are an essential diagnostic feature of EPS. However, EPS needs to be distinguished from other causes of such symptoms including paralytic ileus and other intestinal obstructive conditions and other causes of gastrointestinal symptoms. Changes in peritoneal membrane transport characteristics are frequent [3-5]. Typically, ultrafiltration capacity falls and there is an increase in peritoneal membrane small solute transport prior to development of EPS. However, absence of these changes does not exclude a diagnosis of EPS. A rise in peritoneal membrane small solute transport and loss of ultrafiltration are commonly observed in patients on long-term PD, the majority of whom do not develop EPS. Other presentations include haemoperitoneum and sterile non-resolving or recurrent PD “peritonitis”. Markers of an inflammatory state including elevated C-reactive protein, anaemia and hypoalbuminaemia may be present, but there are no specific diagnostic effluent or blood markers for EPS. Gradual development and chronicity of clinical features is an important diagnostic aspect.

Characteristic macroscopic appearances are observed at laparotomy or laparoscopy. Histological changes that are characteristic of EPS have been described, but are not specific and overlap with membrane changes occurring in long-term PD with ultrafiltration failure and infectious peritonitis [6,7]. Thus “opportunistic” peritoneal biopsy at the time of incidental abdominal surgery in absence of other features of EPS may be misleading.

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Guideline 1.2 - Radiological diagnosis of EPS

CT scanning is recommended as the diagnostic imaging modality of choice. However, mild peritoneal membrane changes on CT without encapsulation or gastrointestinal dysfunction do not make the diagnosis of EPS (GRADE 1B).

Rationale

When a patient on PD presents with abdominal symptoms that are suspicious of EPS, the role of imaging is to confirm the diagnosis and exclude other causes of the symptoms. Most patients will receive a plain abdominal x-ray, and this may be of value in confirming or excluding the presence of bowel obstruction. If bowel obstruction is present, there will be a high suspicion of EPS, but in the absence of peritoneal calcification the diagnosis should not be made on plain film alone.

Of the techniques available, CT scanning is probably of greatest value [1-5]. It is widely available, and has the greatest reproducibility. Therefore, when trying to establish a diagnosis of EPS, CT scanning is recommended as the first line investigation. Reporting should be done by individuals with experience of diagnosing EPS. The features that have a high degree of agreement between radiologists are peritoneal calcification, bowel wall thickening, bowel tethering, and bowel dilatation [5]. Where additional information is required for planning of surgery, small-bowel barium studies are recommended to assess for the presence of strictures [1,2].

Ultrasound has the potential to be a valuable diagnostic tool due to its excellent spatial resolution [6]. However, it has two major limitations. Firstly, it is operator dependent and therefore may not be reproducible, and secondly, there is a limitation to the depth of penetration of the sound, meaning that thorough interrogation of the peritoneal cavity may not be possible. Ultrasound must be undertaken with fluid present in the peritoneal cavity.

MRI scanning is relatively untried in EPS. There are potential advantages to using MRI scanning, which is not dependent upon ionising radiation, as fibrotic tissue returns a low signal which should provide excellent contrast in relation to adjacent structures [7]. Potential disadvantages include bowel peristalsis causing image degradation, slightly lower spatial resolution when compared with CT scanning and need to administer gadolinium-based contrast agents (which have been associated with nephrogenic systemic fibrosis in renal failure). It currently seems unlikely that MRI will gain a main stream role in the diagnosis of EPS.

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2. EPS GUIDELINES 2 (2.1 – 2.6)

Guideline 2.1 – General principles of management of EPS

EPS is a complex condition, whose optimal management requires integrated care with input from PD physicians, nurses, surgeons, dietitians, radiologists and intensive care physicians (GRADE 1B).

Guideline 2.2 – Management of nutrition in EPS

Early dietetic referral and careful monitoring of nutritional status, with nutritional support by oral enteral, or often parenteral supplementation is essential (GRADE 1B).

Audit measure

Time from diagnosis to dietetic referral, method of nutritional support provided to patients with EPS, and indices of nutritional status.

Rationale

Gastrointestinal symptoms, with reduced nutritional intake, and the inflammatory catabolic state present in EPS can lead to the development of severe malnutrition [1]. Malnutrition is a crucial factor in the morbidity and mortality associated with EPS. Patients should therefore be referred to a specialist renal dietitian on diagnosis so that early nutrition intervention can be initiated if required.

In severe cases and those with degrees of bowel obstruction, parenteral nutrition (PN) is usually required. Reports on the use of PN either alone or with adjunctive therapy varies from as low as 17% in Korea [2] to as high as 79-88% in Japan [3,4] and 82% in Australia [5]. Where PN was the sole source of nutrition, mortality rates reported are 29% [2] and 100% [4]. In patients where bowel function does not recover with

time, home parenteral nutrition may be required. Conservative management of bowel obstruction may require passage of a drainage nasogastric tube for symptomatic control, and intravenous fluid replacement.

In milder cases, nutrition support may be managed with an energy dense diet and where necessary, prescription of oral nutritional supplements and anti-emetics. In cases where patients are unable to tolerate sufficient oral intake, nasogastric or nasojejunal feeding may be indicated. There are currently no published studies reporting on the use of these other methods of nutrition support. It is important that the significant risk of refeeding syndrome is recognised in these patients [1]. NICE guidelines [6] on refeeding syndrome should be adhered to when managing these patients.

Nutritional status should be monitored regularly to assess the effect of the nutritional intervention. Due to the presence of abnormal fluid balance and ascites in many of these patients, weight alone is an insufficient marker. Handgrip strength, mid arm circumference (MAC), mid arm muscle circumference (MAMC) and subjective global assessment are all suitable alternatives.

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Guideline 2.3 – Drug treatment for EPS

There is no clear evidence to support a recommendation for the use of any medical therapy for treating the inflammatory and fibrotic features of EPS.

Corticosteroids, immunosuppressants and tamoxifen have been used, and may be tried at the physician's discretion (GRADE 2C).

Audit measure

Use of specific anti-inflammatory, anti-fibrotic or immunosuppressive drug treatment in the management of cases of EPS.

Rationale

There is no clear evidence-based drug therapy for treating the inflammatory and fibrotic features of EPS. The rarity of the condition means that there are no randomised controlled trials of drug therapy. The natural history of EPS is variable with some patients improving with conservative measures alone. Thus small observational series or case reports of drug treatment, without control patient data, are difficult to evaluate. Corticosteroids are the most commonly used and reported therapy, but the evidence is very limited. In 1995, a Japanese Ministry of Welfare working group proposed steroids as a potential therapy for EPS, leading to their widespread use in Japan. A report of experience from one unit in Japan suggests an improvement in survival following introduction of steroids for treatment of EPS (0/6 survival prior to use of steroids in 1997 and 5/5 survival after) [1]. However, with these small numbers, and other possible improvements in management over this time, a beneficial effect of steroids cannot be concluded from this report. In a 4 year prospective Japanese study of 1958 PD patients, EPS occurred in 48 patients [2]. Although this study reports 0% recovery for treatment with PN alone, compared with 38.5% for those receiving corticosteroids and 58.3% for surgical treatment, the PN alone group comprised only 3 patients, so inferiority of PN alone compared with steroids cannot be assumed from this data. In contrast, in a series of 15 cases from Japan, with PN alone 5/15 developed remission and 4 died, whereas 6 patients receiving steroids all subsequently failed to improve and required surgery [3]. A large recent UK series showed no difference in outcomes for patients treated with steroids, immunosuppression, tamoxifen or combinations of these, compared with those who were not [4]. Any beneficial effect of steroids may be most likely to occur at an earlier, inflammatory stage of the disease [5].

There are a small number of reports of therapeutic responses of EPS to immunosuppressants, including cyclosporin and azathioprine – either as direct therapy, or at the time of transplantation [6]. However, many of these patients also received corticosteroids, and EPS can actually develop following renal transplantation in patients already receiving these drugs.

There is interest in the use of tamoxifen in EPS, based on its effectiveness in other fibrotic conditions and case reports and small series suggesting therapeutic benefit in EPS [7-11]. Tamoxifen avoids the catabolic and immunosuppressive effects of corticosteroids and other immunosuppressants in a condition where malnutrition and sepsis are important determinants of mortality [11]. However, evidence is limited and tamoxifen has its own specific side-effects.

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Guideline 2.4 – Referral for surgical management of EPS

Patients should be referred/discussed early with surgical units who have expertise in EPS surgery. Surgery should be performed by teams experienced in EPS surgery, dealing with a high rate of referral / operative procedures* (GRADE 1B).

***(Units at Manchester Royal Infirmary and Addenbrooke's Hospital, Cambridge have been designated as national referral centres for surgery relating to EPS in England from 1st April 2009 by the NCG (National Commissioning Group) and referrals from outside England may be accepted. A patient referral pathway is being developed for suspected cases).**

Guideline 2.5 – Indications for surgical management of EPS

Surgery is indicated where clinical features of EPS fail to resolve with ongoing conservative medical and nutritional therapy. Indications include recurrent subacute or persistent bowel obstruction, failure of nutritional status to respond to conservative therapy, intraperitoneal haemorrhage and peritonitis (GRADE 1B).

Audit measures

Numbers of patients referred for specialist surgical review, whether this was at an NCG-approved centre, and the underlying reasons in cases where this was not felt appropriate.

Indications for operation in patients undergoing surgery, survival and return of gastrointestinal function and nutritional and symptomatic improvement in cases treated medically and surgically and overall.

Number of patients with EPS presenting for emergency surgery.

Rationale

There is increasing evidence that surgery has an important and definitive role in the treatment of EPS [1,2]. In experienced hands, surgery results in high rates of improvement in symptoms and survival. Surgery should be done in a setting where the surgical team has experience with and understands the condition, and has proper peri-operative renal and intensive care support. Surgical units at Manchester (Mr

Titus Augustine), and Cambridge (Mr Chris Watson) have been designated as national referral centres for surgery relating to EPS in England by NCG (National Commissioning Group). Referrals from outside of England may also be accepted. Indications for surgery include non-responsiveness to medical treatment, bowel obstruction (acute and recurrent subacute), intraperitoneal bleeds, and peritonitis. The decision to operate should be taken when there is a combination of the above indications, though intestinal obstruction and peritonitis may in themselves be absolute indications. A surgical opinion should be sought early after diagnosis. Surgery should be timed so that it is considered after an adequate trial of medical therapy and before the patient is too decompensated nutritionally and metabolically.

Patients are admitted prior to surgery for preoperative evaluation and nutritional support. PN, as advised by a dietitian experienced in management of PN in renal patients, should be commenced prior to surgery in nutritionally deficient patients [3,4]. Anaemia is corrected by transfusion and renal replacement, where required is provided by haemodialysis. Ideally, surgery should be done electively or semi-electively on a planned list. Peritonectomy done as an emergency is associated with a high mortality and morbidity from enteric perforations and haemorrhage. There should be an experienced anaesthetist capable of dealing with renal failure patients.

Surgical management in EPS endeavours to tackle the underlying patho-physiological process. Encapsulation of the gut leads to malabsorption, sub-acute and recurrent obstruction and in advanced cases, complete mechanical obstruction, internal herniation, and strangulation leading to peritonitis, septic shock and mortality. The membrane is also inflamed, leading to a chronic inflammatory process, anaemia and major haemorrhage may occur from the membrane. Careful laparotomy is performed (bowel may be adherent to the thickened parietal peritoneum of the anterior abdominal wall, and hence it is important to review CT scans prior to surgery to identify a safe area to enter the peritoneal cavity). Ascitic fluid is drained and careful dissection of sclerotic peritoneum from abdominal wall performed. Careful dissection of thickened peritoneum from bowel loops is undertaken, with the aim to achieve a balance between maximal removal of sclerotic membrane from the bowel wall, whilst avoiding inadvertent perforation. If there is an inadvertent enterotomy, a proximal diverting stoma should be made, as primary closure, or resection and anastomosis will

invariably break down. If a stoma is made, it is important to note the length of small bowel proximal and distal to the stoma. In an emergency situation, with bowel gangrene or with significant intra-abdominal sepsis, a laparostomy may be used with delayed abdominal closure. Surgery may be associated with the need for large volume transfusions and fluid shifts.

Postoperatively an intensive care bed is mandatory. Patients may require ventilation and haemofiltration/haemodialysis after surgery. PN is continued until bowel movement returns and the patient is able to take and maintain nutrition orally. Nutritional supplements and NG/NJ feeding may need to be continued until nutritional status improves. If there is a jejunostomy / ileostomy at <200cm length, short gut guidelines for oral / nasogastric feeding should be considered / adapted depending on renal function [5]. If there is ≥ 75 cm small bowel distal to the stoma, fistuloclysis may be considered [6]. These measures can relieve or ease requirement for PN until stoma reversal is possible.

Postoperatively, intra-abdominal collections may occur which may be radiologically drained. There is a recurrence rate of approximately 20% after surgery which may require repeat surgery.

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Guideline 2.6 – Management of PD after diagnosis of EPS

PD should usually be discontinued after diagnosis of EPS with transfer to haemodialysis. However, in symptomatically mild cases, patient life expectancy and quality of life should be considered in individual cases before switching to haemodialysis (GRADE 2C).

Rationale

PD should usually be discontinued after diagnosis of EPS and the patient transferred to haemodialysis. However, some cases of EPS are clinically less severe and potentially could worsen on stopping PD. Thus the life expectancy of the individual patient should be taken into consideration when considering discontinuation of PD. Generally the PD catheter is also removed, though some patients in Japan have been managed by leaving the catheter in situ with regular peritoneal lavage [1]. It is unclear whether this has any beneficial effects by removing mediators of the peritoneal fibrotic process, or whether the catheter and irrigation fluid could act as a further stimulus to the EPS process.

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3. EPS GUIDELINES 3 (3.1 – 3.2)

Guideline 3.1 – Post-transplant EPS

The incidence of post-transplant EPS is low, so this should not deter use of PD in patients who are candidates for renal transplantation, or transplanting patients on PD (GRADE 1B).

Rationale

Discontinuation of PD is a stimulus for the development of some cases of EPS, with a significant proportion developing after renal transplantation [1, 2]. Although a report from 2 Dutch units suggested an increase in numbers of cases over a 2 year period (2004-5), the number of cases was small and there is no clear evidence of a genuine, sustained increase in the occurrence of post-transplant EPS [1,3]. The incidence is low, so this condition should not be a deterrent to the use of PD in patients who are candidates for renal transplantation, or to transplanting patients on PD. Studies show

overall comparable or favourable outcomes of renal transplantation in patients on PD compared to those on haemodialysis.

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Guideline 3.2 – Management of post-transplant EPS

General principles of diagnosis and management of EPS also apply when it develops following renal transplantation. Differential diagnosis includes transplant-related causes of gastrointestinal disturbance (GRADE 1C).

Rationale

General principles of diagnosis and management of EPS also apply to episodes developing following renal transplantation. Differential diagnosis includes transplant-related causes of gastrointestinal disturbance such as use of mycophenolate mofetil as immunosuppression, infections and post-transplant malignancy.

4. EPS GUIDELINES 4 (4.1 – 4.2)

Guideline 4.1 – Switching of dialysis modality in long-term PD

Routine pre-emptive switching to haemodialysis after a specified time on PD is not recommended (GRADE 1C).

Rationale

The incidence of EPS increases significantly with time on PD, particularly after 5 or more years of treatment [1,2] but the optimal approach to patients on long duration PD is unclear. The majority of long-term PD patients will not develop EPS. Pre-emptive switching to haemodialysis could potentially be associated with development of EPS rather than being a preventive action and there is no prospective data demonstrating benefit of such a policy. Modality switch could have significant

adverse psychosocial and medical implications for patients, which need to be considered on an individual basis. With improvement in management and outcome of EPS, there is a less strong incentive to stop PD pre-emptively to try to prevent development of EPS. Decisions on continuation of PD in long-term patients should be made on an individual basis, and also consider factors determining patient and technique survival, such as frequency of peritonitis, clearance including residual renal function, peritoneal membrane function, ultrafiltration and potential for transplantation.

References

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- [2] Kawanishi H, Kawaguchi Y, Fukui H et al, for the Long-Term Peritoneal Dialysis Study Group. Encapsulating peritoneal sclerosis in Japan: a prospective, controlled, multicenter study. *Am J Kidney Dis* 2004; 44: 729-737

Guideline 4.2 – Screening for EPS

Routine clinical, biochemical or radiological screening in long-term PD patients cannot be used to identify features of early or imminent development of EPS (GRADE 1C).

Rationale

At present the limitations of radiological techniques do not allow the diagnosis of “early” EPS. There is no evidence that regular screening of long-term PD patients by radiological techniques can detect pre-symptomatic EPS or beneficially alter PD management. CT scans coincidentally performed in PD patients prior to development of EPS do not show features indicating developing EPS [1].

References

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