

Perianal Crohn's Disease

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Abstract

Perianal Crohn's disease refers to the involvement of the anal region in this chronic inflammatory bowel disease. It most commonly presents with the formation of perianal abscesses and fistulas, although other forms of presentations such as fissures and skin tags may also be present. Perianal activity often parallels abdominal disease activity, but may occasionally be the primary site of active disease, and significantly compromises the quality of life in affected patients. The primary treatment of patients with perianal Crohn's disease combines medical and surgical management with the aim of improving quality of life and alleviating suffering. A multidisciplinary approach involving the patient, surgeon, gastroenterologist, radiologist, pathologist, nutritionist, and other specialists makes the successful treatment of PCD possible. This paper reviews the management of patients with perianal Crohn's disease, focusing on contemporary medical and surgical treatments such as infliximab, endorectal advancement flap, instillation of fibrin glue, and the potential use of extracellular matrix plugs.

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Crohn's disease is a chronic relapsing and debilitating inflammatory bowel disease of unknown etiology. Perianal Crohn's disease refers to the involvement of the perineal area in this inflammatory process. It may be present in 5–25% of Crohn's patients and can be associated with active disease in the proximal gastrointestinal tract or colon in about one-third and half of the patients, respectively [1].

Perianal Crohn's disease most commonly presents as perineal abscesses and fistulas, which are frequently multiple, complex and recurrent. Rectovaginal fistulas may occur in 3–10% of women with CD, more often in the mid-portion of the rectovaginal septum, and are challenging to treat [2]. PCD may also present with fissures, anal ulcers, edematous skin tags, fecal incontinence and anal stenosis; rarely, it may also be associated with cancer. The perianal disease activity frequently parallels intestinal flare-up, although about 5% of patients may predominantly suffer from anal symptoms with quiescent abdominal disease [3]. In some cases, perianal disease may be the presenting symptom of CD, preceding the abdominal symptoms, and leads to the diagnosis of CD [4].

Diagnosis

The diagnosis of PCD in patients with known history of CD presenting with anorectal complaints is obvious. However, Crohn's disease should also be suspected in patients with multiple and complex perianal abscesses and fistulas, non-traumatic rectovagi-

nal fistulas, recurrent non-healing eccentric fissures and persistent perineal wounds. In the presence of known or suspected PCD, diagnostic efforts are frequently focused on defining the type, location and nature of perianal involvement.

Thorough history and physical examination

History and physical examination are often sufficient for a diagnosis of most perianal lesions, and specialized imaging studies are not routinely required. In severe cases, rectal examination may be limited because of significant anal pain and tenderness. In a case of suspected undrained perineal sepsis, examination under anesthesia should be performed immediately. Imaging and other diagnostic modalities, such as endoscopy, ultrasound, contrast studies, computerized tomography and pelvic magnetic resonance imaging can help in the diagnosis and classification of PCD [5]. These techniques may help to locate undrained abscesses not evident on physical examination, and are useful to delineate the number and location of perianal fistulas, associated collections, relation to the sphincter mechanism, and secondary fistula tracts. Careful attention to these factors is essential to correctly tailor treatment to suit each patient.

Transanal endoscopic ultrasound

EUS is most sensitive for the detection of abscesses and fistulas [6]. The interpretation of this examination is user-dependent, and the accuracy of EUS in the detection of perianal fistulas may be enhanced by the use of hydrogen peroxide. EUS findings may change the surgical management in 10–15% of cases [7]. In cases where severe anal tenderness precludes a digital rectal examination, transanal EUS without anesthesia is usually not possible.

Static transperineal ultrasound

This new modality for assessing the perianal region [8,9] uses an ultrasound transducer which is applied on the perineal skin. The procedure is less invasive than conventional anorectal EUS and may be informative also in cases that severe anal pain and tenderness. Preliminary results are encouraging, but future experience is needed to determine whether this modality is effective in the evaluation of PCD.

PCD = perianal Crohn's disease

CD = Crohn's disease

EUS = endoscopic ultrasound

Endoscopy

Endoscopy is essential to identify active proctitis and colitis, take biopsies from any suspicious lesion of the anal canal and rectum, and may help to locate internal openings of perianal fistulas draining to the lower rectum.

Perianal Crohn's disease most commonly presents with perianal abscesses and fistulas, and significantly jeopardizes patients' quality of life

Gastrograffin or barium enema and conventional fistulography

These are helpful to localize fistulas and associated collections or secondary tracts, but they cannot define their relationship to the sphincter mechanism [10].

Pelvic computerized tomography

Pelvic CT may be informative regarding perianal abscesses not seen in the physical examination, as well as regarding the extent of perirectal sepsis and proctocolitis. However, it is not accurate for perianal fistulas and is not routinely used for this purpose.

Pelvic MRI

Pelvic MRI with phased-array or endoanal coils is accurate for classifying Crohn's perianal fistulas [11]. The diagnostic accuracy of this test is at least similar to that of EUS and EUA. A prospective study from the Mayo Clinic in Rochester, Minnesota, showed that pelvic MRI, rectal EUS, and EUA are all reasonably accurate ways of classifying PCD. The researchers [12] suggest that the optimal approach in patients with CD and suspected of having a perianal fistula or abscess may be the combination of any two of the three methods.

Medical and surgical treatment

Since Crohn's is a chronic disease, it is currently unrealistic to expect any therapy to be curative. The main goal of both medical and surgical therapies is to improve and maintain quality of life. Perianal disease is frequently associated with significant patient suffering and morbidity, which affects daily activity and severely compromises quality of life. The correct diagnosis of the perianal condition and prudent use of the various medical and surgical treatment options are paramount in the treatment of these patients.

A multidisciplinary approach involving the patient, surgeon, gastroenterologist, radiologist, pathologist, nutritionist, and other specialists enables the successful treatment of PCD. The acute and long-term management of such patients depends on knowledge of the type and location of lesions, the sites involved,

diagnostic modalities, perianal anatomy, the severity of the patient's symptoms, and medical and surgical options. Moreover, the general condition of the patient and proximal intestinal tract should also be evaluated and treated if necessary. Several studies suggested that if perianal manifestations persist in the presence of proximal luminal disease, resection of the inflamed bowel can alleviate perianal disease, but its practical use is still controversial [13,14].

The primary treatment of such patients combines medical and surgical management, with the aim of improving quality of life and alleviating suffering. A comprehensive multidisciplinary approach is fundamental, as either one alone is frequently not efficacious.

Medical treatment

Prior to selection of medical treatment, thorough identification of the site of fistula tracts, exclusion of perirectal abscess and evaluation for the presence of active proctocolitis are advised. Current medical therapy includes antibiotics, azathioprine and 6-mercaptopurine, infliximab, cyclosporine, and tacrolimus. Corticosteroids are usually not beneficial in the therapy of PCD and may retard wound healing and exacerbate abscess formation [15]. Aminosalicylates are also ineffective for closing fistulas. However, treatment of active rectal inflammation with topical corticosteroids or mesalamine may improve anal symptoms.

Treatment options combine medical and surgical management. A multidisciplinary approach is essential for the successful treatment of perianal Crohn's disease

- **Antibiotic therapy.** There are no controlled trials showing that antibiotics are effective in the treatment of Crohn's perianal fistulas [16]. Currently, metronidazole and ciprofloxacin are the main agents used for up to 3–4 months. The response rate may reach 80%, but long-term therapy is required to prevent exacerbation. Adverse events resulting from prolonged use of metronidazole may, however, limit its use.
- **Antimetabolites such as azathioprine and 6-mercaptopurine.** These are widely used in current clinical practice. A meta-analysis of controlled trials and uncontrolled case series showed that in 54% of patients the fistula healed after 4 months of therapy and in 95% the fistula may be healed with 9 months of treatment, but exacerbation is common after discontinuation [17].
- **Cyclosporine A.** Uncontrolled case series have suggested that using intravenous cyclosporine for 7 days leads to an im-

EUA = examination under anesthesia

provement in 83% of patients, but high exacerbation rates after conversion to oral therapy [18]. Severe side effects such as renal insufficiency, hypertension, infection, hepatotoxicity, paresthesias and seizure are associated with cyclosporine, and its use is not routinely indicated for perianal Crohn's disease.

- *Infliximab*. This is a mouse-human chimeric monoclonal antibody against tumor necrosis factor. Controlled trials have shown that infliximab administered as a triple-dose induction regimen at 0, 2 and 6 weeks is associated with at least a 50% decrease in purulent discharge of the fistula [19,20]. Maintenance therapy with infliximab every 8 weeks may prolong the time to loss of response and is required in many patients for long-term symptom control [16]. The treatment is generally well tolerated and widely used in patients unresponsive to antibiotics and antimetabolites. The gradual development of anti-chimeric antibodies against infliximab frequently requires an increase in the dosage, and may eventually lead to drug tolerance and loss of effectiveness.
- *Tacrolimus*. A recent small placebo-controlled trial showed that tacrolimus given for 10 weeks reduced the number of draining fistulas without complete closure [15]. Although not used routinely, tacrolimus may be a potential therapeutic agent in patients not responding to azathioprine, 6-mercaptopurine or infliximab [21].
- *Urgent and emergent surgery*. Control of perineal sepsis and abscesses requires EUA for diagnosing the source of sepsis, and draining simple or deep abscesses without fistulotomy of an associated fistula. If a fistula is identified a non-cutting Seton (non-absorbable suture) is inserted through the fistula tract to ensure continuous drainage, leading to the resolution of the perianal sepsis. Premature removal of Seton increases the incidence of recurrent perianal sepsis.
- *Elective surgical treatment*. Elective surgery for PCD may include procedures for non-fistulous complications such as dilatation of anorectal strictures. Most commonly, however, patients with PCD will require surgery to repair perianal and rectovaginal fistulas not responsive to medical therapy, which may include fistulotomy, fibrin glue injection, transanal endorectal flap advancement and gracilis muscle interposition. Occasionally, temporary diverting colostomy or ileostomy is required to control symptoms, and in extremely severe cases resistant to both medical and surgical therapy, proctectomy or proctocolectomy may be required [23].
- *Treatment of fistulas*. Treating fistulas in patients with PCD is challenging because of poor wound healing and risk of secondary incontinence. The selection of a surgical approach largely depends on the type of fistula, past attempts at repair, severity of symptoms, and current continence.

Surgical treatment

The goal of surgical treatment in PCD is to improve quality of life and offer effective palliation, and is reserved for patients who develop perianal complications of the disease or are unresponsive to aggressive medical therapy. CD tends to progress despite surgical therapy, and most patients will require at least one operation during their lifetime [22].

Surgical treatment of PCD can be divided into two main categories: urgent and emergent treatment, which is mainly aimed to control perineal sepsis by adequate drainage; and elective treatment of sequelae of the disease such as perianal fistulas and anal strictures. Similar to abdominal surgery for Crohn's disease, the perineal procedure should be effective enough to control sepsis or alleviate suffering, but not so aggressive as to cause sphincter function damage.

Collaboration on surgical intervention with the gastroenterologist, radiologist, pathologist, nutritionist, and other specialists is crucial for successful therapy, especially if the patient has active proximal luminal disease. These patients are often immunocompromised, malnourished and sick, and the correction of diarrhea, dehydration and electrolyte imbalance, nutritional status and adrenocortical insufficiency is essential prior to surgical intervention. Active proximal luminal inflammation should be appropriately treated with the aim of reducing stool liquidity which irritates the perianal area.

New medical and surgical treatment modalities such as infliximab, endorectal advancement flap, instillation of fibrin glue, and extracellular matrix plugs may improve symptom control and quality of life

- *A limited fistulotomy*. This can be safely performed only on simple (low) fistulas not including any significant portion of the external anal sphincter, without active proctitis and with well-controlled proximal luminal disease, as well as adequate continence. The fistula tract should be identified, probed throughout its length, and intraoperatively assessed prior to the decision to proceed with fistulotomy. Following adequate assessment, the fistula is laid open using electrocautery, and the fistula tract is curetted. Rectovaginal fistulas should not be treated with fistulotomy in patients with PCD, even with low fistulas, due to the risk of incontinence. In women, the anterior part of the anal sphincter mechanism is shorter and weaker than the posterior, combined with the absence of the puborectalis muscle at this region, and any division of the sphincter mechanism may lead to a significant impairment in continence [24]. Complex (high) fistulas require a non-aggressive surgical procedure to avoid

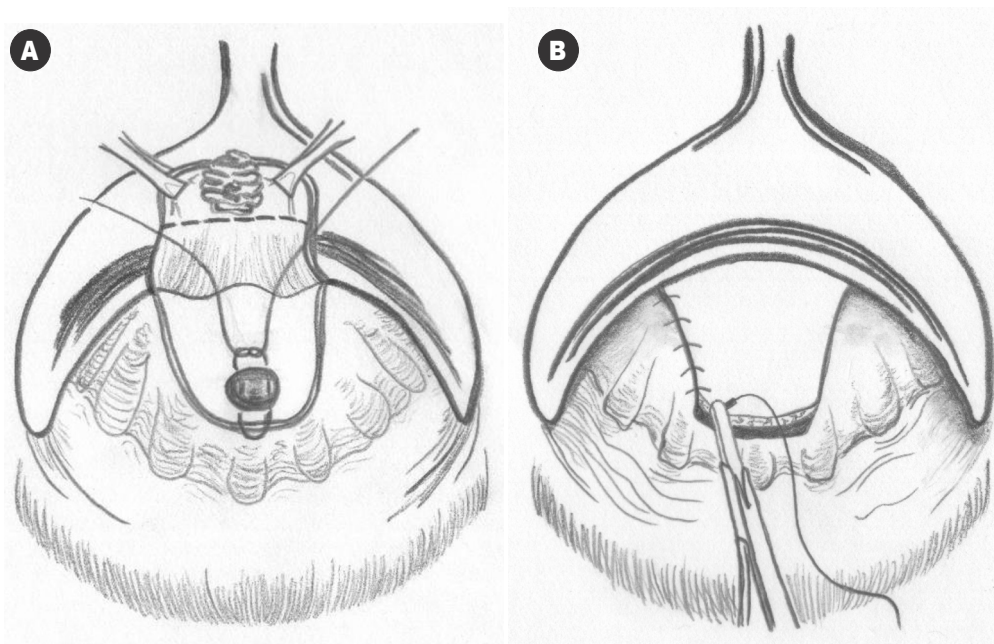


Figure 1. Endorectal advancement flap for the repair of perianal fistula. [A] Creation of the flap. [B] Covering the internal opening of the fistula.

destruction of the sphincter mechanism. A non-cutting Seton is most commonly used [25,26]. It provides drainage of the fistula tract and may be left in place for a long time until the inflammation is quiescent.

- *Endorectal advancement flap.* This is a surgical technique to repair perineal fistulas with the preservation of anal sphincter function. The principal idea of this procedure is to surgically close the internal opening of the fistula using a flap made of rectal wall, allowing the healing of the fistula from inside out. Since a pliable and well-healing rectal flap is crucial, this procedure may be performed only when no active proctitis is evident, and may be especially helpful in anteriorly located and rectovaginal fistulas in women [27,28]. Using an operative anoscope, a broad-based, U-shaped incision of the rectal wall is made and a flap of lower rectum is raised [29]. The internal opening of the fistula is closed using sutures, and the flap is pulled down and sutured to cover the internal opening. The external tract is curetted and enlarged for adequate drainage [Figure 1].

The reported success rate of endorectal advancement flap in patients with Crohn's perianal fistulas ranges from 25 to 100% in different series, with an average success of approximately 50–60% [27,30,32]. However, endorectal advancement flap is not a minimal procedure; it requires training, and may be associated with a moderate rate of postoperative complications.

- *Instillation of fibrin glue.* This technically simple procedure for the treatment of perianal fistulas is associated with low risk and early return to normal activity. Fibrin glue is a blood product that uses the activation of thrombin to form a fibrin

clot, mechanically sealing the fistula tract. The clot induces tissue-healing processes while being gradually absorbed by fibrinolysis. Following probing of the fistula through its entire length, a soft catheter is inserted into the fistula tract, and the glue is slowly injected while gradually withdrawing the catheter, until the glue completely fills the fistula tract [Figure 2].

Series using fibrin glue for perianal fistulas of mixed etiologies have yielded success rates of approximately 30–70%. There are currently no series addressing the use of the glue specifically for PCD, but subgroup analysis of series with mixed types of fistulas suggests that the cause of

fistula does not significantly affect the success rate [32]. An ongoing Israeli multicenter study is currently aiming to assess the use of fibrin glue, combined with induction of temporary local remission using infliximab, for Crohn's disease-associated perianal fistula, and the results of this



Figure 2. Instillation of fibrin glue into the fistula tract. The double-armed syringe is inserted through the external opening and the glue is injected into the tract.

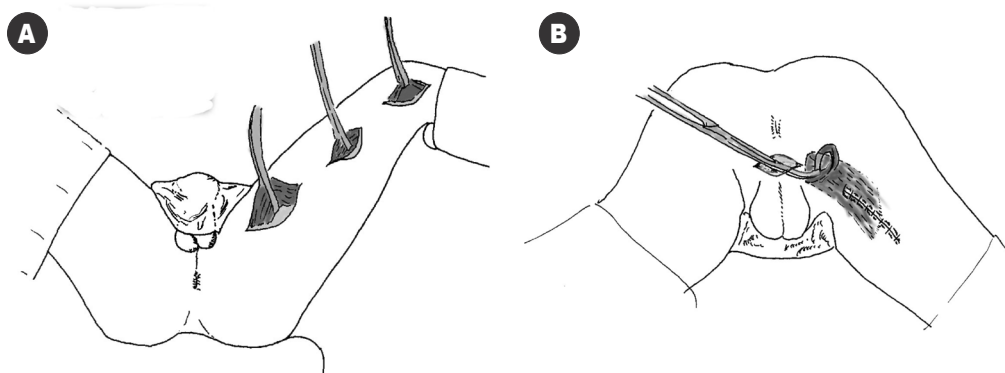


Figure 3. Gracilis muscle transposition for the repair of perianal fistula. **[A]** Thigh incisions. **[B]** Perianal incision and muscle transposition.

study may help determine the role of fibrin glue in the treatment of these patients.

- *Extracellular matrix plug.* This product was recently introduced for the repair of perianal fistula. The plug is made of biomaterial harvested from porcine small intestine and contains extracellular matrix made of collagen and other biologic substances. When introduced into the fistula tract, it provides a scaffold for connective tissue growth to repair the fistula. The surgical procedure itself is technically simple and associated with low risk and early return to normal activity. A recent study of a series of 20 Crohn's patients with 36 fistulas reported a success rate of 83% [33], but larger series are required to define the role of this new modality in the treatment of patients with Crohn's disease.
- *Gracilis muscle transposition.* This is a major procedure used for the repair of perineal fistulas in patients with severe symptoms who failed simpler procedures, and is especially helpful in the treatment of persistent rectovaginal and rectourethral fistulas. The principal idea of this procedure is the use of the gracilis muscle, rotated as a flap to the perianal area, to interpose between the rectum and adjacent organs, such as the vagina and the urethra, bringing a thick viable tissue to separate the two sides of the fistula. The gracilis muscle, which is normally located at the medial aspect of the thigh, is detached from its attachments near the knee, and dissected free through three small thigh incisions. The plane between the rectum and the vagina or urethra is then dissected to divide the fistula tract, and the gracilis muscle is rotated and sutured to interpose between the rectum and the vagina or urethra [Figure 3]. The success rate with this procedure for Crohn's rectal vagina fistulas is approximately 70% [34].

Extensive perianal fistulas associated with active proctitis, severe recurrent perirectal sepsis or rectovaginal fistulas, in which perineal procedures are unsuccessful, may require creation of a temporary diverting ileostomy or colostomy. Fecal diversion

alleviates suffering associated with the perianal disease, at the expense of quality of life due to the stoma. Diversion may also allow healing and closure of perineal fistulas, and avoids the risk of persistent non-healing perineal wound frequently associated with proctectomy [35]. However, in highly selected patients with severe uncontrolled perineal sepsis and active proctitis in spite of aggressive medical and surgical treatment, proctectomy may be performed as a last resort to improve quality of life.

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Labor to keep alive in your breast that little spark of celestial fire called conscience

George Washington (1732-1799), first U.S. president

Capsule

Antibiotic prevents complications of measles

Prophylactic co-trimoxazole given to children with measles reduces the incidence of pneumonia (odds ratio 0.08, 95% confidence interval 0-0.56) and conjunctivitis, and positively affects weight gain in the month after infection ($P = 0.04$), say Garly and colleagues. They randomized 84 patients in Guinea-Bissau with measles to either receive the antibiotic or a placebo

for 7 days after diagnosis. They saw a non-significant trend towards less diarrhea, severe fever, oral thrush, and stomatitis in the group treated with antibiotic, but no difference in rates of otitis media between groups.

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Eitan Israeli

Capsule

Oxytocin quiets the brain at birth

Birth entails a multitude of transitions. Studying rats, Tyzio and colleagues identified yet one more, a link between oxytocin exposure and the switch in how certain brain neurons fire. The neuro-transmitter GABA is usually excitatory in fetal brain neurons but inhibitory once they mature. Exposure to oxytocin

during parturition causes a switch from excitation to inhibition in GABA signaling. This quieting of neuronal activity may serve to protect the brain against transient hypoxia during birth.

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