Current Problems in Surgery 57 (2020) 100808

Contents lists available at ScienceDirect

Current Problems in Surgery

journal homepage: www.elsevier.com/locate/cpsurg

Fistulizing Crohn's disease

Amy L. Lightner[a,*], Jean H. Ashburn[b], Mantaj S. Brar[c,d,e], Michele Carvello[f], Pramodh Chandrasinghe[g], Anthony de Buck van Overstraeten[c,d,e], Phillip R. Fleshner[h], Gaetano Gallo[f], Paulo Gustavo Kotze[i], Stefan D. Holubar[a], Lillian M. Reza[g], Antonino Spinelli[j,k], Scott A. Strong[l], Philip J. Tozer[g], Adam Truong[h], Janindra Warusavitarne[g], Takayuki Yamamoto[m], Karen Zaghiyan[h]

Introduction

Crohn's disease (CD), characterized by idiopathic transmural inflammation anywhere along the gastrointestinal (GI) tract, is increasing in incidence worldwide for unknown reasons. The transmural inflammation can result in inflammatory, stricturing, or penetrating (fistulizing) phenotypes, all of which are notoriously difficult to treat. When a patient has inflammatory disease, medical immunosuppressive therapy with corticosteorids, immunomodulators, or biologics may be helpful before a fibrostenotic disease process starts. Once there is fibrosis, bowel damage is difficult to reverse, and proximal fistulizing disease may develop. Fistulizing disease, one of the most notoriously difficult disease manifestations can also occur anywhere along the GI tract, affecting portions as proximal as the duodenum or as distal as the anus with perianal and rectovaginal fistulas (RVFs).

From the [a]Department of Colorectal Surgery, Digestive Disease Surgical Institute, Cleveland Clinic, OH; [b]Department of Surgery, Wake Forest University Baptist Medical Center, Winston-Salem, NC; [c]Department of Surgery, Mount Sinai Hospital, Toronto, ON; [d]Zane Cohen Center for Digestive Diseases, Toronto, ON; [e]Department of Surgery, University of Toronto, ON; [f]Department of Medical and Surgical Sciences, University of Catanzaro, Catanzaro, Italy; [g]Fistula research Unit, St Mark's Hospital and academic institute, London, UK; [h]Department of Surgery, Cedars Sinai, Los Angeles, CA; [i]IBD Outpatient Clinics, Colorectal Surgery Unit, Catholic University of Parana (PUCPR), Curitiba, Brazil; [j]Humanitas Clinical and Research Center, Colon and Rectal Surgery Unit, Italy; [k]Humanitas University, Department of Biomedical Sciences, Italy; [l]Department of Gastrointestinal Surgery, Northwestern University, Chicago, IL; and [m]Inflammatory Bowel Disease Center & Department of Surgery, Yokkaichi Hazu Medical Center, Yokkaichi, Japan

* Correspondence to: Amy Lightner, MD, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195.
E-mail address: lightna@ccf.org (A.L. Lightner).

https://doi.org/10.1016/j.cpsurg.2020.100808

Unfortunately, fistulas represent a frequent manifestation of CD, affecting up to 50% of patients. Fistulizing CD includes perianal (55%), entero-enteric (24%), RVF (9%), entero-cutaneous (6%), entero-vescical (3%), and entero-intrabdominal (3%) fistulas.

The presence of perianal fistulizing CD (PFCD) should be considered as a distinct disease phenotype from luminal fistulizing disease and, according to some authors, is a marker of increased disease severity if present at initial diagnosis, with faster progression from an inflammatory phenotype too a stricturing/penetrating pattern, thereby requiring a multidisciplinary approach. The modified Parks classification describes the perianal fistula tract in relation to the external anal sphincter and crucially influences the management (medical or surgical). The number of external openings, fluctuation, presence of RVF fistula, and/or rectal stricture has been also included into "classifying" perianal CD by the American Gastroenterological Association in order to improve the therapeutic strategy.

The etiology of fistulizing CD is largely unknown, but it is considered the result of multifactorial interplay between genetic, immune-related, environmental, and infectious factors. The transmural inflammation predisposes CD patients to fistula formation, but the first step in this process is generally assumed to be tissue destruction. In particular, increased tissue levels of tissue growth factor beta (TGF-β) produce epithelial-to-mesenchymal cell transition and matrix metalloproteinases alter the structure of the tissue, leading to fistula formation.

In this monograph, we discuss the epidemiology of fistulizing disease, the various anatomical locations of fistulizing disease, and various treatment approaches to provide an overview of an important, and difficult to manage, phenotype of CD.

Epidemiology, Classification, and Pathophysiology

CD is a chronic inflammatory bowel disease (IBD) that can affect the entire GI tract, including the anus, and can be complicated by the development of fibrotic strictures, perforation, abscess formation, and fistulization. The most common age at diagnosis is between 15 and 30 years, with a second peak between 50 and 70 years.[1] CD is one of the most expensive diseases to treat,[2] representing a socioeconomic burden with substantial direct and indirect costs to the healthcare system and society.[3]

Fistulizing CD comprise perianal (55%), entero-enteric (24%), RVF (9%), entero-cutaneous (6%), entero-vesical (3%), and entero-intrabdominal (3%) fistulas.[4] Perianal manifestations of CD were first described by Bissell in 1934,[5] 2 years prior to subsequent description of perianal fistulas by Burrill Crohn's in 1936,[6] who actually failed to mention the link between regional enteritis and perianal disease.

A few years later, after the first report on CD, Morson and colleagues[7] described the presence in some patients of perianal non-caseating granulomas and fistulas several years before the onset of intestinal CD. In fact, it has been demonstrated that perianal fistulas may even precede the diagnosis of CD by some years.[8]

Epidemiology

The incidence of CD worldwide ranges between 0.1 and 16 per 100,000 population per year,[9] with no association with gender[4,10] or body-mass index[11], and with a north to south gradient detected in Europe.[12] Perianal fistula represents a frequent manifestations affecting up to 50% of patients with CD,[4,13-15] with a lifetime risk that has been reported to be between 20% and 40% in referral IBD centers.[16-19]

The presence of PFCD is definitely to be considered as a distinct disease phenotype and, according to some authors, is a marker of more severe disease if present at initial diagnosis, with a faster progress from inflammatory to stiucturing or penetrating and requiring different therapeutic strategies.[20] In fact, according to Eglinton and colleagues[21] the mean age at the time of

diagnosis was 8.1 years younger for those with PFCD ($P < 0.0001$), with a significatively longer disease duration in the perianal disease group.

In several population-based cohorts studies, the incidence of PFCD patients is estimated to be between 13% and 28%[4,22-25] and in approximately 10% of patients is the initial manifestation of CD, independently from luminal inflammation,[4,22-25] although 95% of patients develop perianal fistulas in parallel with luminal disease.[26] Moreover, a population-based study by Schwartz and colleagues stated that the cumulative incidence 10 years after the diagnosis of CD was 33%, and 50% after 20 years.[4]

Data are inconsistent regarding the prevalence of PFCD in patients with racial and ethnic differences.[27] A retrospective study of 830 patients recruited from 6 different centers showed that African Americans were more likely to develop PFCD compared with Caucasians.[28] These results were consistent with those reported in the study by Cosnes and colleagues,[29] in which non-Caucasian race appears to be associated with PFCD. Conversely, in a cross-sectional study conducted in all adult patients with CD treated with infliximab (IFX) there were 88 out 333 (29.3%) patient with perianal disease. Among those patients, 54.5% were white, 20.5% were African American, 22.7% were Hispanic and 2.3% were Asian.[30]

The incidence of PFCD may be associated with luminal disease location as the finding of PFCD is 3 times greater in patients with Crohn's colitis than those in with ileitis.[25,30] In this context, perianal fistulas were reported in 12% of patients with small bowel CD, 15% with combined ileocolonic CD, 41% with colonic CD without rectal involvement, and 92% of CD with rectal involvement.[4,23,25,30]

Another frequent form of the penetrating disease is represented by RVF. RVF remains the most challenging manifestation of PFCD and may occur in 5.2%-10 % of patients comprising the second major cause of RVF behind obstetric trauma.[31,32] The majority of CD RVF are low or even anovaginal and may arise from rectal ulcerations or infection of anterior anal glands.

Fistula-associated tumors are rare but increasingly reported and mucinous adenocarcinoma (59%) is the most common malignancy described in long-standing chronic perianal fistulas, followed by squamous cell carcinoma (31%).[32,33]

Classification

Perianal fistulas are traditionally classified using the anatomical nomenclature described by Parks and colleagues.[34] This classification was based on their location with respect to the external sphincter. Other classifications, such as St. James's Hospital classification[35] or Cardiff classification,[36] have been used but have been abandoned for their difficult use in daily clinical practice as well as for a low level of evidence.[37] Regardless, in a subset of patients with CD, the penetrating nature of the disease can bring gradual destruction of the sphincter with subsequent incontinence. For this reason, perianal fistulas require a separate subclassification, being a predictor of more aggressive disease course in patients with CD.

The Vienna Classification[38] for CD does not mention perianal and luminal fistulae, but the recent Montreal classification provides a modifier for perianal disease,[39] underlining the impact of the disease manifestation. In order to improve the therapeutic strategy and the prognosis, the American Gastroenterological Association (AGA) proposed a new 5-item classification dividing perianal fistula into simple or complex (Fig 1, Table 1) considering anatomical position, the number of external openings, fluctuation, the presence of RVF fistula, and/or rectal stricture.[13]

Pathophysiology

The etiology of CD remains largely unknown, but it is considered the result of a multifactorial interplay between genetic, immune-related, environmental, and infectious factors. Current theories suggest an aberrant mucosal immune response to commensal gut flora in genetically susceptible individuals.

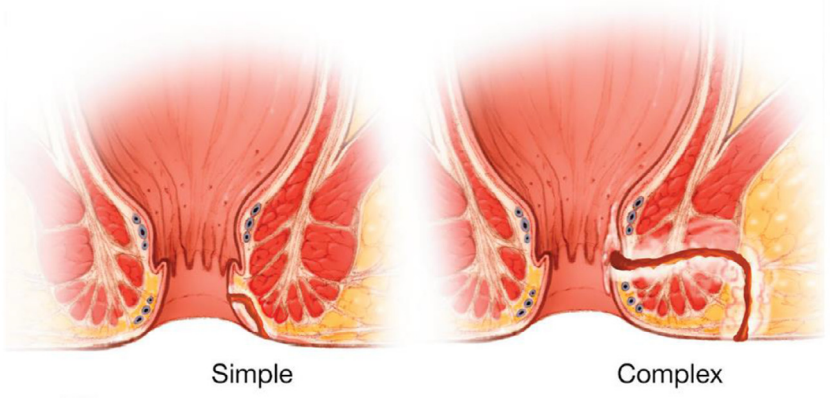

Fig. 1. American Gastroenterological Association (AGA) classification of Perianal fistulizing crohn's disease. Adapted from Sandborn et al.[40] by Kotze et al.[41]

Table 1
American Gastroenterological Association (AGA) classification of perianal fistulizing Crohn's disease.

	Simple fistula	Complex fistula
Anatomical position (above or below the dentate line)	Low	High
External opening	One single	Multiple
Pain/fluctuation	Never	May be associated
Rectovaginal fistula	Never	May be associated
Anorectal stricture	Never	May be associated

The transmural inflammation predisposes CD patients to fistula formation, but the first step in this process is generally assumed to be tissue destruction. In this context, several studies suggested the role of epithelial-to-mesenchymal-transition (EMT) as a driving force behind the development of fistulizing CD with TGF-β the principal inducer of EMT. In fact, 70% of CD fistula tracts are covered by a thin basement membrane layer of myofibroblast-like cells, the so-called "transitional cells," that show mesenchymal features,[16] as a result of the downregulation of epithelial cell specific proteins such as E-cadherin, and upregulation of mesenchymal cell proteins such as alpha smooth muscle actin and vimentin.

EMT was first described in 1908 by Frank Lillie[42] and plays a major role in both physiological and pathological processes, such as embryogenesis, organ development, wound healing, tissue remodeling, and cancer progression. During EMT epithelial cells lose apicobasal polarity and epithelial-specific cell contacts, gaining properties of mesenchymal cell, (ie, enhanced motility and cell spreading).[43] The reduced migratory potential of CD fistula tract cells stimulate the migration of epithelial cells towards the defect undergoing EMT with the aim of repair the mucosal barrier. These processes could be an attempt of the intestinal nonimmune cells to close deep tissue defects and result in the formation of transitional cells with both epithelial and mesenchymal cell markers.

Myofibroblasts can also contribute to fistulizing CD by secreting matrix metalloproteinases, bringing an aberrant healing process and tissue destruction.[44] Unfortunately, further studies are needed to confirm the role of EMT due to the demonstration of similar results in non-CD fistulae.

Recently, the introduction of genome-wide association study led to the identification of many genetic loci as well as new mechanisms such as autophagy undoubtedly with a undoubetedly role in CD pathogenesis. However, the contribution of this genetic loci alone is modest without an interplay with other factors.[45] A nucleotide-binding oligomerization domain containing 2 (NOD2), also known as caspase recruitment domain-containing protein 15, is the first identified

CD susceptibility gene.[46] It is an intracellular protein, encoded by the NOD2 gene located on chromosome 16, involved in controlling commensal bacterial flora in the intestine.[47] Primarily, NOD2 is required for optimal innate immune signaling and its inactivation can bring to a dismissed bacterial killing. Current evidence suggests that the NOD2 gene variant is the most well-established genetic variation linked to the onset of CD, playing a role in 27% of patients with CD.[48] Other genetic variations in genes such as ATG16L, IRGM, IL23R, TNFSF15, and OCTN (IBD5) have strongly been linked with CD.[48] In particular, the IBD5 haplotype variants were strongly associated with perianal complications of CD.[49]

Summary

CD is a severe chronic and potentially debilitating GI disease that represents a heavy burden for patient's quality of life and the healthcare system. Unfortunately, the etiology remains incompletely understood even if it is generally accepted that it results from a complex interaction between an aberrant immune response and genetic, environmental, and microbial factors.

Fistulas are a frequent manifestation that may develop in approximately one third of patients with CD. In this context, perianal fistula has been shown to be a distinct disease phenotype being associated with distal intestinal involvement and a more severe CD course. For this reason, a good subclassification is crucial to improve the therapeutic strategy and the prognosis.

Perianal Fistulizing Disease

Presentation and Symptoms

Initial Presentation

Overall, 26% of patients with CD have perianal disease, and typically present to their gastroenterologist or directly to colorectal or general surgeons with complaints of one or several of the following signs and symptoms: new warm, erythematous, painful perianal lump, with or without drainage.[22] If the patient is already on medical therapy for CD, they may have atypical presentations and lack some of the aforementioned signs and symptoms. Patients may complain of pelvic pain alone. These patients clinically have an un-drained perianal or ischiorectal (eg, perirectal) abscess and require an examination under anesthesia (EUA) for source control. Rarely, patients with new or known fistulizing perianal CD may present dramatically with necrotizing fasciitis of a perianal source, often in the thigh or vulvar area.[50,51]

The most common presentation for patients with known CD, who typically present or call their gastroenterology team, is intermittent perianal drainage. The disease process follows a cyclical course of quiescence, followed by swelling and pain, spontaneous drainage, then resolution and quiescence. Clinically, these patients have a fistula-in-ano.

There is a subgroup of patients who do not carry a diagnosis of CD who have complicated fistulizing perianal disease, presumably cryptoglandular in origin. These patients have typically already undergone multiple operations and been referred to a colorectal surgeon. They are evaluated for CD with colonoscopy, enterography, and laboratory studies (C-reactive protein, fecal calprotectin), referred to a gastroenterologist, and ultimately it is found that 5% of CD patients have isolated perianal disease with the diagnosis typically made by the colorectal surgeon in combination with the multidisciplinary team.[4]

Subsequent Presentations

After the initial presentation, future presentations typically are of the intermittent perianal drainage type mentioned above, often in close proximity to a prior seton, fistulotomy, incision and drainage site, or other surgical procedure. However, in contrast to purely cryptoglandular patients, CD patients, upon new or subsequent presentation, may present atypically and tend to

"break the rules" both for initial and subsequent presentations. Specifically, it is often observed that Goodsall's rule may not apply, with curvilinear and radial tracts, with side-sinus tracts, circumferentially.[52]

Patients with penetrating proctocolitis may present with pelvic pain and purulent drainage per ani, and the index of suspicion may prompt one of the imaging modalities noted below to diagnose a supralevator abscess preoperatively.[53]

Immunosuppressed Patients

Great care should be taken in immunosuppressed patients with perianal disease. These patients may present in a more protean manner and harbor occult large ischiorectal or supralevator abscesses without the typical signs of sepsis. When these patients present, and there is an adequate index of suspicion, every effort should be made to either proceed directly to the operating room for an EUA and incision and drainage, and it is not unreasonable to obtain fast-track imaging, preferably a pelvic magnetic resonance imaging (MRI) fistula protocol, or pelvic computed tomography (CT) scan, especially if one suspects a supralevator abscess.[54]

Preferred Imaging and Diagnostics

MRI Fistula Protocol

For patients with recurrent and complex fistulizing perianal CD, dedicated pelvic MRI, after a proper EUA (ie, with dilute hydrogen peroxide, etc.) is most helpful as an adjunct to delineate complex fistulous anatomy.[55] This technology, with high-powered fields of view, T1, T2, LAVA, fat-saturation, and other sequences, with an experienced radiologist, has a very high sensitivity for differentiating various fistulous features.[56] These include internal/external sphincter involvement, fistula side branches (eg, sinus tracts), anovaginal vs RVF fistulae, undrained fluid collections, the presences of setons, and burnt out fibrotic sinus tracts.[57]

There are several roles for MRI in patients with CD. The first is preoperatively in patients presenting with suspected complex fistulae to (1) provide a road map for the EUA and (2) as a baseline study which can be used for future comparison in patients with complex fistulae in the setting of future flares and exacerbations. The second is postoperatively, as an adjunct to (thorough) EUA, while on medical therapy – typically with draining seton(s), for identification of occult disease in patients whose disease is refractory to combined medical and surgical therapy. Thus, MRI of the pelvis is especially useful in patients with a more aggressive penetrating phenotype.

Finally, we note that the vast majority of patients with CD will have active or quiescent bowel involvement, and often when they are having a perianal flare they will have concurrent active proctocolitis and or enteritis.[58] At this time MR enterography (MRE) may be performed concurrently with MR of the pelvis, given that the fistula protocol with high-powered fields of view and dedicated sequences are not compromised.

Endorectal Ultrasound (ERUS)

Endorectal ultrasound, especially when combined with EUA, has a sensitivity and specificity approaching 100%. However, in the modern era pelvic MRI is preferred for several reasons including the fact that it is less invasive, operator independent, and the images are somewhat harder to interpret than MRI. That being said, ERUS definitely has a role in the assessment of the anal sphincter complex and defects, such as after gynecologic and other traumatic injury to the internal sphincter and external sphincter. The utility of ERUS is increased when 3-dimensional ultrasound is applied.[59]

CT Scan

Although pelvic MRI/MRE is preferred for the assessment of fistulizing perianal/enteric CD, especially in the elective setting, during off-hours in the emergency department an abdominopelvic CT scan with and without contrast is often obtained.[58] This may be very help-

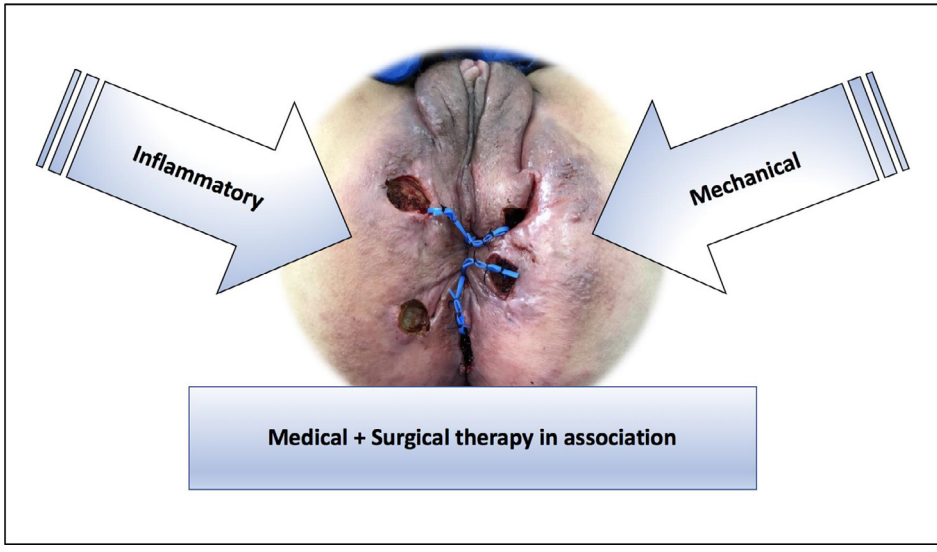

Fig. 2. Main target components in perianal fistulizing Crohn's disease and need for a combined medical-surgical approach.

ful in delineating moderate to large ischiorectal and supralevator abscesses, and even perianal abscesses, but is less helpful for fistulae.

Of note, CT enterography (CTE), especially at IBD centers utilizes low radiation protocols with one third of the radiation of traditional protocols, thus increasing its utilization. That being said, MRI of the pelvis with fistula protocol is preferred for perianal disease and if needed, we recommend combined MRI/MRE.

Anorectal Manometry (ARM)

Similar to ERUS, anorectal manometry has a role in assessing, indirectly, current functional capacity of the anal sphincter complex and in ruling out pelvic floor dysfunction. There is consensus that pregnant patients with active perianal CD are best served by caesarian section, and for those with prior peripartum sphincter injury, in conjunction with ERUS, ARM can provide adjunct data to individualize surgical decision making in these and other at-risk patients.[60] The goal, in the setting of a current or potentially compromised sphincter complex, is to minimize the risk of fecal incontinence given the specter of iterative small or large bowel loss and chronic diarrhea.

Flexible Endoscopy

Colonoscopy obviously has a key role via intubation of the terminal ileum to assess for terminal ileitis, but colonoseapy, as well as flexible sigmoidoscopy/proctoscopy, with rectal biopsies is also useful in assessing for active or microscopic proctitis. Active proctitis is generally a contraindication to more definitive surgical procedures such as endorectal advancement flaps. Colonscopy also has an evolving role in the assessment of squamous cell neoplasia as an alternative/variation of high-resolution anoscopy when combined with methylene blue dye, especially given the increasingly recognized association of fistulizing perianal CD with anorectal cancer.[61]

Medical Therapy

Currently, the pathophysiology of PFCD is based on 2 different components: inflammatory and mechanical (Fig 2). Medical therapy targets the inflammatory component whereas surgery addresses the mechanical component. Treating both in combination leads to better outcomes for CD patients.

Table 2
Summary of conventional medical therapy in the management of perianal fistulizing crohn's disease.

Medication	Year of publication	Author	Type of study	Number of patients	Efficacy with agent	Efficacy with placebo
AZA/6-MP	1995	Pearson et al.[64]	Meta-analysis	41	54%*	21%*
Metronidazole	2009	Thia et al.[62]	Randomized controlled trial	7	0%†	12.5%†
Ciprofloxacin	2009	Thia et al.[62]	Randomized controlled trial	10	30%†	12.5%†

* Clinical remission.
† clinical response and remission.
AZA, azathioprine; MP, mercaptopurine.

There are clear limitations regarding conventional medical therapy for the management of perianal fistulas in CD. Steroids and aminosalicylates do not have any efficacy in perinaal fistulizing CD and are not indicated in any treatment algorithms.[37] Antibiotics such as metronidazole and ciprofloxacin have also been tested in this phenotype of CD, again with limited efficacy.[62] Their use is often associated with symptom improvement, but long-term antibiotic monotherpay is limited due to adverse events and poor efficacy. The use of antibiotics in combination with other classes of medications (eg, anti-TNF agents) in complex fistulas improves symptomatic response and prevents abscess formation. A prospective evaluation of ciprofloxacin with adalimumab vs adalimumab alone demonstrated higher rates of fistula closure with combination therapy compared to adalimumab monotherapy alone.[63]

Despite worldwide adoption of thiopurines for CD, there is lack of evidence regarding thiopurines (azathioprine and 6-mercaptopurine) in the setting of PFCD. One meta-analysis demonstrated a clinical response rate of 54% with azathioprine compared to 21% with placebo, but that deserves careful interpretation.[64] The use of thiopurines as monotherapy in PFCD is currently not recommended, but their association with anti-TNF agents leads to encouraging results in clinical response. Calcineurin inhibitors (as cyclosporine) and methotrexate are not recommended as first-line agents in PFCD. Findings of conventional therapy are summarized in Table 2.

Anti-TNF agents such as IFX and adalimumab (ADA) are considered the most effective class of medical therapy in the management of perianal fistulas in CD. IFX was studied prospectively in 2 specific trials that included exclusively a population of patients with fistulizing disease. Present and colleagues demonstrated the efficacy of IFX by a reduction of 50% of fistula drainage (68% in patients with 5 mg/kg vs 26% in placebo; $P= 0.002$) and complete fistula healing (55% with 5 mg/kg vs 13% in placebo; $P= 0.001$).[65] Sands and colleagues in the ACCENT II trial described longer time to loss of response to IFX in patients maintained with the agent in a dose of 5 mg/kg every 8 weeks compared to placebo (>40 weeks vs 14 weeks; $P < 0.001$). After one year, complete fistula healing was observed in 36% of receiving patients under IFX compared with 19% with placebo ($P= 0.009$).[66]

Data with ADA in the management of PFCD comes from further analysis of the CHARM trial and other small studies. A meta-analysis which included 7 studies with 379 patients demonstrated efficacy of this agent in treating perianal fistulas secondary to CD.[67,68] Complete fistula closure was observed in 36% of the cases (95% CI: 0.31-0.41) and partial fistula response was described in 31% of the cases (95% CI: 0.031-0.61). The only prospective evaluation with ADA in the management of PFCD is derived from the ADAFI trial, which was designed to test concomitant ciprofloxacin in efficacy, with similar numbers in terms of response and closure.[63] Data from certolizumab pegol is also derived from further analysis of the PRECISE trial, where fistula healing was observed in 36% of patients with the drug compared to 17% with placebo ($P= 0.038$).[69] Data with other biologics with different mechanisms of action, such as vedolizumab and ustekinumab, are limited and these agents are not considered as first line biologics in patients with PFCD. In addition recent evidence suggests higher efficacy in patients with higher serum levels, raising the question if the dose for PFCD with anti-TNF agents should be the same as luminal disease, for example.[70] A summary of the efficacy of anti-TNF agents in PFCD is described in detail in Table 3.

Table 3
Main studies with efficacy data from anti-TNF agents in perianal fistulizing Crohn's disease.

Agent	Year of publication	Author	Type of study	Fistula closure/ response as primary endpoint	Number of patients on anti-TNF agent	Fistula closure (%)
IFX	1999	Present et al.[65]	Randomized controlled trial	Yes	94	55%
IFX	2004	Sands et al.[66]	Randomized controlled trial	No	282	36%
ADA	2009	Colombel et al.[67]	Post-hoc analysis	No	70	60%
CZP	2011	Schreiber et al.[69]	Post-hoc analysis	No	28	36%

IFX, infliximab; ADA, adalimumab; CZP, certolizumab pegol; TNF, tumor necrosis factor.

It is important to emphasize that therapy with anti-TNF agents is associated with better efficacy and safety outcomes when their initiation is performed after adequate surgical management of the fistulas, with eradication of chronic sepsis in fistula tracts and seton placement, avoiding repeated abscess formation. Results with this combined medical-surgical approach demonstrate better efficacy compared to both medical or surgical strategies alone.[71,72]

Operative Indications

Simple fistulas can typically be treated adequately with a fistulotomy, as they are usually superficial without significant involvement of the sphincter muscles and are not discussed in this session. Different surgical techniques, however, are indicated for the management of complex PFCD, and aim to resolve the mechanical component of this disease phenotype. The rule of thumb for different surgical techniques in the management of complex perianal fistulas in CD is that those are indicated exclusively in the absence of active proctitis. This means that optimal medical therapy is needed before any surgical attempt, to achieve rectal mucosal healing and preferably with epithelialization and reduced inflammation of the fistula tracts.[41]

EUA with adequate perianal hygiene, curettage of all granular tissue inside fistula tracks, eradication of chronic sepsis, and placement of loose setons constitute the most frequent surgical approach in PFCD patients (Fig 3). Virtually all patients with complex fistulas require this approach, before initiation of biological therapy, in order to avoid the closure of the external opening at the skin level which can lead to repeated perianal abscesses. The results with this approach can lead to complete healing after simple seton withdrawal in approximately 50% of patients, without the need for a secondary surgical procedure.[71] The withdrawal of setons is only indicated after complete mucosal healing of the rectum and improvement in local inflammation at the tracts. The frequency of repetition of this procedure and intervals between operations is decided in agreement between the gastroenterologist and the colorectal surgeon.

Once the mucosa is healed in the rectum, the seton is withdrawn and there is persistence of the fistula tract with epithelialization, with little or no inflammation; additional surgical procedures are needed in order to close the internal opening and heal the fistula (correcting the mechanical component). The most common procedure that can be indicated is the rectal advancement flap. In this procedure, the surgeon gently dissects a segment of healthy tissue proximally to the internal opening, creating a thick U-shaped flap with a wide pedicle that maintains adequate blood supply. After cleansing and closure of the internal opening, the flap is sutured with absorbable interrupted stitches in the anal canal, covering the internal opening adequately. Successful results vary from 50% to 100% and are based on small retrospective case series from different countries, according to a systematic review.[73] It is generally agreed that the results with the advancement flap are more promising in cryptoglandular as opposed to Crohn's fistulas.

Another technique that can be used in specific cases is a Ligation of the Intersphincteric Track (LIFT) procedure. This approach was first described by surgeons in Thailand and is constituted on the identification, isolation, and simple ligation of the fistula tract between sutures. Despite initial excitement, this is a procedure that is difficult to be widely used in clinical practice, as most of the PFCD patients present with tracts that have multiple associated sinuses and

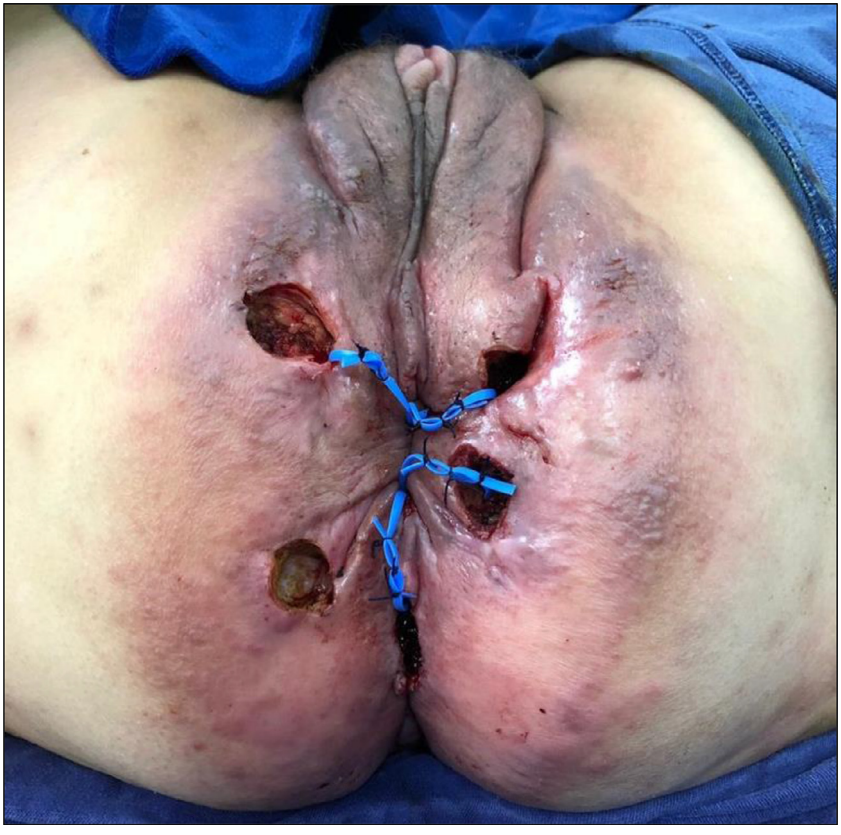

Fig. 3. Seton placement and perianal hygiene in a CD patient with complex perianal CD.

secondary extensions. A retrospective analysis of a prospective database of 23 CD patients who underwent the LIFT procedure demonstrated fistula healing in 48% (11/23) of patients; the median time for failure was 8 months. Patients with small bowel CD had higher rates of LIFT healing (P= 0.04) and patients with colorectal CD had higher rates of LIFT failure (P= 0.02).[74] Despite being an adequate option with promising results, the LIFT procedure has precise indications in complex PFCD.

Fibrin glue and anal fistula plugs were also tried in the management of complex fistulas in CD patients. The GETAID group published the results of a prospective trial comparing fibrin glue with observation after seton withdrawal in CD patients. Despite encouraging results, these findings were not reproducible in clinical practice, and therefore the technique has not been widely adopted for the management of CD-related fistulas.[75] The same pattern occurred with the anal fistula plug. A prospective trial from the same GETAID group demonstrated no difference with the use of the plug as compared to seton withdrawal alone. Clinical remission was observed in 33.3% of the complex fistulas and 30.8% of the simple fistulas in the plug group compared to 15.4% and 25.6% in controls, respectively (RR = 2.17 in complex fistulas and RR = 1.20 in simple fistulas; P= 0.45).[76] The use of the plug in CD-related fistulas is currently not typically utilized in clinical practice for perianal CD.

Two other techniques, with a similar principle, can also be applied in the management of PFCD. The VAAFT (*video-assisted anal fistula treatment*) is basically a minimally invasive procedure in which a fistuloscope is inserted in the tracts, with initial mapping of the secondary extensions, followed by excision of the granular tissue and cauterization of the whole tracts

in association with stitching of the internal opening. Initial results in a small case series were promising.[77] However, despite an association with symptomatic improvement, the role of this procedure in PFCD still needs to be determined in comparison with other techniques, and more data are needed. The FILAC (*fistula laser closure*) is conceptually similar to the VAAFT procedure, despite not incorporating direct visualization of the whole fistula tract. The principle is to burn the tract in its whole extension circumferentially with a laser probe after primary closure of the internal opening, healing the fistula.[78] Again, the results in CD-related fistulas come from small case series, and this method still must be better studied prospectively in comparison to other techniques.

Despite all of the advances in surgical strategies over the last decades aimed at fistula healing, a significant proportion of patients will fail different techniques and will evolve toward anorectal stenosis, sphincter damage, and low quality of life, needing a diverting ostomy to improve symptoms. Only 16% of patients diverted will have successful resolution of symptoms on stoma closure. Unfortunately, the reality is that a proctectomy is still performed in 41% of patients.[79]

Stem Cell Therapy

Even with the best combined medical-surgical management of perianal fistulas in CD, complete healing is only achieved in 50%. This lack of healing demonstrates the need for novel approaches in the management of PFCD.

The use of mesenchymal stem cells (MSC) to treat CD-related perianal fistulas was first described by a Spanish group, in a phase I trial.[80] There are basically 2 types of MSCs that can be used as local therapy for PFCD: allogeneic (cells are harvested from a non-CD healthy donor) or autologous (cells are harvested from the same CD patient). Allogeneic MSCs from healthy donors have the advantage of having improved immunomodulatory properties compared to those from a CD patient.[81] In addition, complex procedures associated with harvesting, isolating, conditioning, and storing the cells before use are not needed for each patient as is the case when autologous cells are used. The potential advantage of autologous MSCs is the lack of alloimmunity (antibodies to the cells), in what could become a theoretical attraction towards their use, although there are no studies demonstrating alloimmunity with allogeneic cells, either. There are no comparative studies between these 2 different MSCs in the IBD field.[82] Currently, allogeneic MSCs are mostly used in research protocols, and are even commercially available in Europe, as a pharmaceutical product.

The ADMIRE-CD trial was a large phase III study designed to evaluate the efficacy of MSCs in clinical and radiographic healing of perianal fistulas in CD. The MSC product tested was Cx601 (darvadstrocel), a 24 mL solution with 120 million expanded adipose-derived allogenic MSCs.[83] All patients had an EUA, with curettage of the fistula tract(s) and seton placement (if needed) 2 weeks before the injection of the MSCs. At the time of cellular delivery, an unblinded surgeon injected darvadstrocel or placebo saline solution (randomized in a 1:1 ratio) in different levels of fistula tracts according to a defined protocol, after closure of the internal opening. The primary objective of the study was combined remission (clinical closure of all treated external openings draining at baseline, and the absence of collections of more than 2 cm confirmed by central reading MRI) at week 24.

After 24 weeks, significantly more patients in the darvadstrocel group achieved combined remission compared to placebo (53/107 [50%] vs 36/105 [34%], respectively; $P= 0.024$). Clinical remission alone (closure of 100% of external openings which were draining), a secondary endpoint, was observed in 57% of the darvadtrocel patients compared to 41% of placebo patients ($P= 0.064$). A total of 66% (68/103) of patients receiving darvadstrocel and 65% (66/102) receiving placebo experienced treatment-related adverse events, including, most commonly, proctalgia, anal abscess, and nasopharyngitis. Treatment-related adverse events were found in 17% of the study group compared to 29% in placebo, and included mostly anal abscesses and proctalgia. Anal abscesses occurred in 5% of the overall patients in both groups.

Outcomes after 52 weeks in the ADMIRE-CD trial were published in another manuscript.[84] In this long-term analysis, the efficacy of darvadstrocel was maintained to 1 year. In the modified

ITT analysis, combined clinical and radiological remission was observed in 58/103 (56.3%) of the darvadstrocel patients, compared to 39/101 (38.6%) of placebo patients; $P= 0.010$). Clinical remission (100% closure of baseline fistulas with active drainage) at week 52 was observed in 59.2% in the darvadstrocel and 41.6% in the placebo group, respectively ($P= 0.013$). No new safety signals were noticed in the additional 24 weeks of this follow-up study. This study led to the approval of the first commercial solution of MSCs to be used in PFCD (Alofisel, Takeda, Zurich, Switzerland) by the European Medicine Agency. The European commercially available solution is constituted of 4 vials of 6 mL of MSCs with 30 million cells each, with a total of 120 million cells. The complexity of the procedures is linked to the short shelf life of cell viability, approximately 48 hours from the laboratory facility to the operating room, and significant costs of the MSCs.

More studies with MSCs to treat perianal fistulas in CD are warranted, as several issues remain unanswered. What is the ideal dose of MSCs to treat complex fistulas? What is the long-term safety of their use? Is the use of a scaffold (anal plug or fibrin glue) an option for better healing of the fistulas? Surely the strategy of cell-based therapy for PFCD will be studied in several ways in the years to come, representing a new hope for healing for CD patients.

Rectovaginal Fistulizing Disease

Presentation, Symptoms, and Anatomic Classification

The altered systemic cellular biology leading to increased epithelial to mesenchymal transition and matrix protein remodeling in intestinal cells in CD can result in intestinal penetration and fistula formation, including RVFs.[85] Up to 9% of all CD patients develop a RVF,[4] with the risk proportional to the frequency and severity of colorectal inflammation.[31,86] These fistulas are notoriously difficult to treat in patients with CD, with various studies reporting recurrence in 25%-80% of patients following treatment.[87]

The presence of a RVF is an extremely morbid condition, with foul-smelling air, stool, or pus discharge from the vagina. The enteric connection to the vagina may additionally cause recurrent urinary tract infections, loss of fecal continence, and abscess formation. Understandably, the psychosocial impact associated with RVFs is immense, including social stigma and high rates of depression[6]. Furthermore, the presence of RVF may cause significant dyspareunia and may impact self-esteem and formation of long-lasting relationships.

One classification system of RVFs is by tract location. Rectovaginal fistulas may be classified as “low” when the vagina connects to the rectum at or below the dentate line (typically 2 cm from the anal verge). The terms “low rectovaginal fistula” and “anovaginal fistula” may be used interchangeably. A “high” RVF opens significantly proximal to the dentate line, connecting to the vagina at the level of the cervix, and a “middle” RVF lies somewhere in between. A key feature of a low RVF or anovaginal fistula is the involvement of the anal sphincter complex. RVFs may also be classified as “simple” or “complex.” A simple fistula is a low, short, small diameter ($<$2.5 cm) tract without branches that is often caused by infection or obstetric injury. A complex fistula may be high, wide, or branching yet may also include any fistula resulting from CD, cancer, radiation, or recurring following treatment failure. This section focuses on RVF fistulizing disease secondary to CD. RVFs are clinically distinct from an anorectal fistula or fistula-in-ano which is similarly associated with CD but provides different symptomatology and treatment options.

Diagnosis and Imaging

A thorough history and physical examination is essential during the diagnostic evaluation. Patients invariably present due to symptoms and further investigation confirms the diagnosis and delineates the anatomy. A thorough visual examination using an anoscope and speculum should be conducted, and digital rectal examination together with bimanual pelvic examination may uncover scars, defects, polyps, or abscess cavities on the anterior rectal or posterior vaginal wall.

Care should be exercised as the affected area is often sore, inflamed, and excoriated. A complete colonoscopy is indicated to assess the proximal colon and terminal ileum. Often, simultaneous vaginal examination during colonoscopy or proctoscopy may reveal audible or visual evidence of gas emanating through the RVF connection.

Imaging is particularly valuable in these patients. MRI is particularly useful in fistula identification because it may visualize the inflammatory reaction around the fistula tract and detect adjacent organ involvement. Retrograde barium enema may also be helpful but has a low sensitivity in RVFs. An alternative is the methylene blue tampon test done by inserting a vaginal tampon and administering a saline or sodium phosphate rectal enema dyed with methylene blue. A RVF fistula is confirmed by blue staining on the tampon. A vaginogram may provide further information, particularly in case with small fistulas. Vaginography involves insertion of a foley catheter into the vagina, inflating the catheter balloon to form a seal, and then filling the vagina with contrast. If done properly, the seal between the vaginal opening and the cervix will provide enough pressure to pass contrast through the fistula tract. Fistulography involves placement of a catheter into one end of the fistula and injecting contrast under pressure to highlight the tract. This has a success rate ranging from 16% to 50% in anorectal fistulas[88] but has been shown to be useful in detecting elusive high non-CD RVF fistulas in case reports.[89,90]

Rectovaginal exam under anesthesia (EUA) may be the most useful diagnostic and therapeutic tool. Examination aided by anesthesia permits a painless and thorough examination of the perineum and pelvic organs. Liberal use of retractors and fistula probes are essential for tract identification. Lacrimal probes are valuable adjuncts as they are thinner and more malleable. Application of hydrogen peroxide may delineate the tract and locate the distal vaginal or rectal opening. Following tract identification, a seton may be inserted to allow conversion of an inflamed fistula to one that may be amenable to medical and/or surgical therapy. In cases of severe proctitis, a draining seton, with or without diverting ileostomy, may serve as a bridge to a less invasive repair, avoiding a total proctocolectomy. Novel diagnostic techniques using a fistuloscope have been popularized by some authors[91] and have recently been used for RVF fistulas by Schwandner.[92] Fistuloscopy offers several advantages including the ability to evaluate fistula tracts endoluminally and identify branch points or abscess cavities. This technique can be used in isolation or as an adjunct during definitive fistula repair.

Medical Therapy

There is no consensus regarding optimal medical treatment for CD-related RVFs. The use of antibiotics is known to improve the quality of life in some CD patients although this therapy does little to aid in perineal fistula healing.[93] Immunosuppression with 6-mercaptopurine,[94] methotrexate,[95] or tacrolimus[96] therapy, used alone or together with antibiotics or sulfasalazines, was reported in 3 studies including 12 CD-related RVFs. Together, these 3 studies report complete healing in one third of patients, partial healing in one third of patients, and no response in the remainder of patients, with little evidence of sustained response.[97] A review of 5 studies including 13 patients undergoing cyclosporine therapy for CD-related RVFs showed an initial response in all patients but a sustained response in less than one half.[98]

Anti-tumor necrosis factor alpha (anti-TNF) therapy, alone or together with other medications, has been studied in CD-related RVF in 9 studies, of which 7 focused on IFX as the main therapy.[99-107] A published review of these studies revealed an aggregate of 78 patients; 41% exhibited complete fistula healing, 22% had partial response and 37% had no response to anti-TNF therapy.[97] Post-hoc analysis of the randomized controlled ACCENT II trial by Sands and colleagues analyzed the efficacy and safety of IFX therapy on CD-related RVF.[105] Patients were treated initially with 3 doses of 5 mg/kg intravenous IFX until week 6. By week 10, 17 (63%) of the 27 RVFs in 25 patients closed. Those who responded to the initial 3-dose IFX regimen were randomized to continued IFX therapy or placebo. The duration of fistula closure was longer in patients receiving IFX therapy (46 weeks) compared to placebo (33 weeks), however similar rates of recurrence were seen at 52 weeks (46% vs 43% respectively).

Few studies, none controlled, have evaluated the role of combined medical and surgical treatment of RvFs fistulas in CD. Although most of these single-institution studies are underpowered, they consistently show that preoperative anti-TNF therapy does not worsen or improve fistula healing rates after surgery.[87,108,109] For example, the study by Narang and colleagues evaluated healing rates following surgical RVF repair, with or without biologic therapy.[87,108,109] Of the 68 patients who were treated with preoperative immunomodulation with IFX or adalimumab, there was no difference in healing rates between those who received any biologic (63%) and those who received none (65%). Additionally, there was no difference between those who received differing biologic therapy (IFX 48% vs adalimumab 55%). Contrary to other studies,[110,111] steroids did not worsen surgical healing in this study.

Surgical Therapy

A large variety of surgical treatments for RVFs are available, however the lack of randomized or prospective studies provides little evidence of the optimal surgical approach in CD. The American Society of Colon and Rectal Surgeons (ASCRS) released clinical practice guidelines in 2016 for the management of perineal pathology.[112] Treatment recommendations for RvFs are at best grade 1C (strong recommendation, low-quality evidence) and specific recommendations for CD-related RVF are absent. Table 4 provides a review of all studies with 4 or more patients undergoing surgical repair of CD-related RVFs. Complicating the analysis, all but 4 of the studies were retrospective and observational,[109,113-115] with not a single study being randomized. Unfortunately, there is no consistency in the reporting of fistula anatomy, fistula complexity, disease activity, bowel preparation, or presence of diverting ostomy. Although some studies concur that the absence of proctitis is critical to the success of a repair.[109,116] Gaertner and colleagues found that active proctitis did not correlate with fistula healing.[117] Usage of mechanical and/or antibiotic bowel preparation varied widely, and no recommendation could be made regarding the value of bowel preparation. Creation of a diverting ostomy was also inconsistent and did not appear to improve healing rates following surgery.[117,118]

An endorectal advancement flap (ERAF), with or without sphincteroplasty, is a commonly performed repair, with healing rates ranging between 0% and 75%.[109,118-122] An ERAF involves mobilizing a tongue of rectal mucosa and submucosa including the fistula opening. The exposed fistula tract is cored out, closed in layers, and the rectal tongue is replaced after trimming the diseased section at the apex. Variations in this technique include the advancement of a circumferential sleeve of rectum (advancement sleeve flap) or a linear advancement flap which involves excising the fistula tract longitudinally perpendicular to the dentate line followed by rectal approximation. An anocutaneous flap (ACF) utilizes similar principles to an ERAF and is accomplished by advancing a tongue of cutaneous tissue cephalad beyond the excised rectal fistula opening. Despite 2 small studies of 10 and 14 patients reporting success rates ranging from 86% to 100%,[123,124] this technique is not widely used. In the largest retrospective study focusing on low-lying CD-related RVFs by Hull and colleagues 35 patients with recurrent low-lying fistulas underwent 3 different types of advancement flaps depending on the burden of rectal disease and fistula characteristics at the time of surgery.[119] With an index surgery success rate of 54% and overall success rate of 69% following repeat procedures for fistula recurrence, Hull and colleagues showed that failure of an endorectal advancement flap should not preclude repeat repair attempts. Furthermore, multiple failed attempts does not guarantee treatment failure. El-Gazzaz and colleagues found no difference in healing rates between patients with 4 to 5 repair attempts vs those with 0-3 attempts.[110]

VAAFT was pioneered by Meinero and Mori and involves using a fistuloscope to identify branching side tracts and eliminating them by electrocautery.[91] This may be done independently for diagnostic or therapeutic purposes, but has been combined with ERAF for CD-related RVFs.[92]

A vaginal advancement flap (VAF) has a theoretical advantage in CD by not including diseased GI tissue in the repair. Since an early case series in 1989 citing its success,[125] numerous studies have used VAFs in low, middle, and high fistulas with success rates ranging from 54%

Table 4
Pertinent studies of patients with Crohn's disease undergoing surgical repair of rectovaginal fistula.

First author (year)	Study design	No of patients	Location of fistulas	% with previous repair attempt	% with active proctitis at repair	Bowel preparation	Surgical intervention (n)	Primary success of index surgery	Ultimate success allowing multiple repair attempts	Maximum number of repair attempts	% with diverting stoma before or created at time of repair	Average follow up (months)
Bandy (1983)[139]	R	10	NR	60%	50%	M	10 EP	70%	NR	NR	10%	25
Jones (1987)[120]	R	10	Low (100%)	NR	Some	NR	10 ERAF	60%	NR	NR	Some	25
Radcliffe (1988)[31]	R	12	Low 9% Mid (17%) High (67%)	Some	NR	NR	5 ERAF 6 ACF 1 EP	67%	75%	NR	25%	118
Heyen (1989)[146]	R	4	NR	NR	NR	NR	4 Local closure	0%	75%	4	0%	NR
Morrison (1989)[125]	R	8	Low (50%) High (50%)	Some	Some	NR	2 ERAF 1 VAF 5 Other	50%	50%	3	50%	8-67
Sher (1991)[128]	R	14	Low (50%) Mid (50%)	21%	NR	M+ABX	14 VAF	NR	93%	NR	100%	55
Hesterberg (1993)[124]	NR	10	Low (100%)	20%	70%	NR	10 ACF	100%	90%	2	70%	18
Kodner (1993)[147]	NR	24	Low (100%)	NR	0%	M+ABX	24 ERAF	71%	92%	NR	0%	7
Macrae (1995)[148]	R	5	Low (100%)	100%	NR	M+ABX	4 ERAF 1 Gracilis	Overall (20%) ERAF (0%) Gracilis (100%)	Overall (40%) ERAF (25%) Gracilis (100%)	3	100%	12
Makowiec (1995)[114]	P	12	Low (100%)	Some	Some	M	12 ERAF	42%	NR	NR	Some	20
Ozuner (1996)[122]	R	47	NR	Some	0%	M+ABX	47 ERAF	68%	NR	NR	NR	31
Hull (1997)[119]	R	35	Low (100%)	100%	3%-14%]	M+ABX	35 ERAF	54%	69%	10	26%	35
Joo (1998)[121]	R	20	NR	Some	0%	M+ABX	20 ERAF	NR	75%	NR	Some	17
O'leary (1998)[116]	R	10	Low (50%) Mid (30%) High (20%)	0%	70%	NR	1 Fistulotomy 2 EP 6 ERAF 1 VAF	60%	80%	3	90%	38

(*continued on next page*)

Table 4 (*continued*)

First author (year)	Study design	No of patients	Location of fistulas	% with previous repair attempt	% with active proctitis at repair	Bowel preparation	Surgical intervention (n)	Primary success of index surgery	Ultimate success allowing multiple repair attempts	Maximum number of repair attempts	% with diverting stoma before or created at time of repair	Average follow up (months)
Penninckx (2000)[118]	R	28	Low/Mid (31%) High (69%)	0%	0%	NR	11 ERAF 13 VAF 4 EP	Overall (57%) ERAF (55%) VAF (54%) EP (75%)	Overall (75%) ERAF (47%) VAF (57%) EP (67%)	4	21%	40
Windsor (2000)[129]	R	15	NR	NR	NR	NR	2 EP 9 ERAF 4 VAF	Overall (40%) EP (0%) ERAF (33%) VAF (75%)	Overall (60%) EP (50%) ERAF (44%) VAF (100%)	5	47%	31
Athanasiadis (2007)[123]	O	37	Low (78%) Mid (8%) High (14%)	22%	30%	M+ABX	56 Total 20 EP 15 Direct closure 14 ACF 7 ERAF	Overall (51%) EP (70%) Direct closure (73%) ACF (86%) ERAF (29%)	Overall (73%)	5	76%	85
Songne (2007)[137]	R	8	NR	25%	NR	M	8 Martius	100%	NR	1	100%	40
Ellis (2008)[134]	R	7	NR	Some	NR	NR	2 LIFT + Mesh 5 Plug	Overall (71%) LIFT + Mesh (50%) Plug (80%)	NR	1	NR	6-12
Fürst (2008)[113]	P	12	NR	100%	NR	NR	12 Gracilis	92%	100%	2	100%	41
Wexner (2008)[138]	R	9	NR	Some	NR	NR	9 Gracilis	56%	NR	2	100%	NR
Ruffalo (2009)[109]	P	52	NR	NR	21%	NR	36 ERAF 23 VAF	Overall (56%) ERAF (56%) VAF (57%)	Overall (81%)	3	35%	109
Schwandner (2009)[115]	P	6	Low (100%)	67%	0%	M	6 Mesh	67%	NR	2	67%	9
El-Gazzaz (2010)[110]	RP	58	NR	NR	NR	NR	47 ERAF 8 EP 2 Glue 1 Plug	NR	Overall (45%) ERAF (43%) EP (71%) Glue (50%) Plug (0%)	8	Some	45
Pinto (2010)[127]	R	77	NR	Some	NR	NR	38 ERAF 6 Gracilis 3 VAF 3 EP 30 Other	NR	Overall (44%)	>3	Some	20

(*continued on next page*)

Table 4 (*continued*)

First author (year)	Study design	No of patients	Location of fistulas	% with previous repair attempt	% with active proctitis at repair	Bowel preparation	Surgical intervention (n)	Primary success of index surgery	Ultimate success allowing multiple repair attempts	Maximum number of repair attempts	% with diverting stoma before or created at time of repair	Average follow up (months)
Gaertner (2011)[117]	R	51	NR	NR	94%	NR	Minor: 35 Seton 8 Glue 4 Plug Major: 8 ERAF 6 EP 4 Martius	NR	Minor (40%) Seton (49%) Glue (0%) Plug (50%) Major (50%) ERAF (50%) EP (83%) Martius (75%)	>2	20%	39
Nosti (2013)[126]	R	6	Low (100%)	33%	NR	NR	1 ERAF 1 VAF + Mesh 5 VAF + Bulking (3 Martius, 1 Gracilis)	Overall (67%) ERAF (0%) VAF + Mesh (0%) VAF + Bulking (100%)	NR	1	33%	5
Kaminski (2016)[74]	R	6	Low (100%)	Some	Some	NR	6 LIFT	33%	NR	1	NR	23
Mege (2016)[140]	RP	4	NR	75%	NR	M	4 Mesh	50%	75%	NR	100%	11
Narang (2016)[87]	R	88	NR	NR	NR	NR	2 Glue 1 Plug 6 EP 9 VAF 53 ERAF 3 OSP 5 Gracilis 9 Martius	NR	Overall (70%) Glue (50%) Plug (0%) EP (33%) VAF (89%) ERAF (68%) OSP (100%) Gracilis (100%) Martius (78%)	3	36%	39
Milito (2017)[136]	R	23	NR	NR	Some	NR	10 ERAF 5 VAF 5 Mesh 3 Martius	NR	Overall (78%) ERAF (70%) VAF (60%) Mesh (100%) Martius (100%)	NR	0	39

ABX, antibiotics; ACF, anocutaneous flap; EP, episioproctotomy; ERAF, endorectal advancement flap; LIFT, ligation of the intersphincteric fistula tract; M, mechanical; NR, not reported; O, observational; OSP, overlapping sphincteroplasty; P, prospective; R, retrospective; RP, retrospective analysis/prospective database; VAF, vaginal advancement flap.

to 93%.[109,116,118,126-129] A prospective study by Ruffalo and colleagues of 52 patients (21% with proctitis at the time of surgery) undergoing ERAF or VAF found no difference in healing rates (healing rate 56% vs 57% respectively).[109]

The LIFT procedure has been used as a sphincter-sparing technique to repair anal fistulas. Initially described in 2006 by Rojanasakul and colleagues the LIFT technique involves dividing the fistula tract between the 2 sphincter muscles without myotomy.[130] A handful of studies have analyzed the results of LIFT on complex fistulas, however the number of patients with RVFs do not exceed 2, and CD status is either unspecified or excluded.[131-133] Ellis published a retrospective series reporting healing in 1 of 2 patients with CD-related RVFs who underwent LIFT with biologic mesh interposition.[134] The only prospective series evaluating the use of LIFT for CD-related fistulas included 2 patients with RVFs.[135] Unfortunately, the success rate was not reported for the RVF subgroup. Kaminski and colleagues published the largest cohort of CD patients undergoing LIFT.[74] Of the 6 patients with low-lying RVFs who underwent LIFT, 2 patients (33%) healed.

Perhaps the greatest success has been seen in surgical techniques involving transposition of tissue in the space between the rectum and vagina to obliterate the fistula tract. The traditional Martius labial flap involves mobilizing the bulbocavernosus muscle via vertical labia majora incision. A popular alternative is the modified Martius flap which involves mobilizing a vascularized adipose tissue flap instead of muscle. The tissue is pivoted dorsally under the ischiocavernosus muscle and secured without tension to the RVF space. The success rate of a traditional Martius flap ranges from 75% to 100% in several studies including 3-9 patients with CD-related RVFs.[87,117,136] One study by Songne and colleagues looked specifically at the efficacy of the modified Martius flap in 8 patients, 2 of which had a history of failed repair. Each patient underwent a modified Martius flap with diverting ileostomy and after a mean follow-up of 40 months, 100% of the fistulas remained closed.[137] Combination therapy with VAF together with a bulking procedure has been explored by Nosti and colleagues.[126] In a retrospective review of 6 patients (2 patients with previously failed repair), they found that both ERAF or VAF failed whereas VAF with either modified Martius or gracilis flap yielded a 100% success rate.

The gracilis muscle interposition graft is another bulking procedure that acts similarly in principle to the Martius flap. A 10 cm incision on the posterior medial thigh is made along a line extending from the adductor tubercle to the medial femoral condyle. The neurovascular pedicle arising from the adductor branch of the profunda femoris vessels is located on the superior anterior portion of the muscle. The muscle is dissected along its width and then transected distally before transposition through a subcutaneous tunnel to the perineum. Reported healing rates following gracilis transposition for CD-related RVFs range from 56% to 100%.[87,113,127,138] Wexner and colleagues retrospectively reported their success with gracilis transposition in CD-related RVF and rectouretheral fistulas. Combined with 100% concurrent ileostomy creation, the primary healing rate was 54%.[138] Another study by Fürst and colleagues prospectively evaluated the results of gracilis muscle transposition in 12 patients with CD-related RVFs which had failed past repair attempts.[113] Their technique involved the wrapping of the rectum with the gracilis muscle, creating a well-vascularized neo sphincter. They reported a 92% success rate following initial surgery, and 100% overall success rate following a repeat gracilis transposition in the 1 patient who recurred.

The most aggressive approach is an episioproctotomy which lays open the entire fistula tract to facilitate healing. There is a risk of incontinence, particularly with high fistulas above the anal sphincter complex, necessitating concominant sphincter repair. Success ranges from 33% to 70%[87,110,117,118,139] and current trends have moved away from this procedure.

Transperineal mesh placement is a unique approach using novel biomaterial. A study by Schwandner and colleagues was the first prospective evaluation of biologic mesh for CD-related RVFs.[115] Successful healing was seen in 4 of 6 patients (67%) after an average follow-up of 9 months. Failure was associated with undrained infection and failure to close the rectal opening. Spurred by this report, use of mesh within the rectovaginal space for RVFs has gained momentum, with several recent studies showing healing rates of more than 75%.[136,140] Minimally invasive options such as fibrin glue or collagen plugs have had some early success,[9,89] but more re-

cent studies report poor healing rates in CD related perianal fistulas.[141] Three studies reviewing the use of glue or plugs in CD-related RVFs report healing rates between 0% and 50%.[87,110,117]

Stem Cell Therapy

Mesenchymal stem cells (MSCs) can be found in a variety of adult tissue including bone marrow and adipose tissue. MSCs modulate the function and proliferation of a broad number of innate and adaptive immune cells making them an attractive therapeutic tool for CD.[142] Additionally, MSCs are considered immune-privileged and express low levels of HLA class I or II molecules, thereby avoiding issues with immune rejection. Injection or implantation of MSCs appear to be cleared shortly after administration suggesting transient paracrine or cell-to-cell contact signaling as the main mechanism of effect.

Mesenchymal stem cell technology has been refined over the course of 15 years. A team from Spain has developed techniques to isolate and expand adipose-derived MSCs (AD-MSCs) from liposuction aspirate. A pure and stable population of AD-MSCs was ensured by robust antigen examination over multiple cell generations. Subsequent case studies and trials have established the safety and efficacy of AD-MSCs for the treatment in CD-related RVFs.

In 2003, Garcia-Olmo and colleagues reported the first treatment of CD-related RVF with AD-MSCs.[143] A 33-year-old woman with a complex anorectovaginal fistula with 5 external holes and communication with the vagina that had failed previous medical and surgical treatments underwent injection of 9×10^6 AD-MSCs into the rectal submucosa followed by suture closure of the rectal fistula opening, VAF for the vaginal opening, and fibrin glue for external openings. The fistula completely healed (including all anorectal branches and the RVF) at 1-week follow-up and remained healed at 9-month follow-up.

A phase 1 pilot study in 2005 by the same group described further refinement of autogenous AD-MSC isolation and expansion.[80] The autogenous AD-MSC inoculate was administered to 5 CD patients with complex perianal fistulas, of which 2 patients had RVF fistulas. One patient had 2 RVFs and the other had 1 RVF with 3 additional enterocutaneous fistulas. Rectal mucosa was injected with 6×10^6 to 20×10^6 autogenous AD-MSC cells followed by VAF and closure of the rectal opening ultimately leading to healing of 2 out of 3 (67%) RVFs.

A follow-up phase 2 randomized controlled trial evaluated the effectiveness of autogenous AD-MSCs (Cx401b) with fibrin glue against fibrin glue-only in patients with anorectal fistulas of both cryptoglandular and CD origin.[143] In aggregate, a significant improvement in healing rates was observed following AD-MSC injection with fibrin glue in contrast to fibrin glue alone (71% vs 16%, respectively, $P < 0.001$). Improved healing rates following AD-MSC injection were not statistically different in CD-related fistulas, however there was a strong trend (5/7 [71%] vs 1/7 [14%], $P = 0.10$). Amongst the 8 women with RVF enrolled (4 with CD), 4 were treated with AD-MSCs (healing occurred in 75%) and 4 received fibrin glue (healing occurred in 0%).[143] The phase 3 randomized double-blind controlled ADMIRE CD trial included 212 patients receiving intralesional allogenic AD-MSCs vs placebo however RVFs were excluded from the study.[83]

Combining known fistula treatments to create a novel therapy, Dozois and colleagues created an adipose-derived MSC-coated fistula plug for implantation within the fistula tract.[144] A phase 1 clinical trial showed that implantation of the MSC-coated fistula plug in 15 patients with non-CD cryptogenic fistulas yielded 3 patients with complete healing, 8 with partial healing, and 4 without improvement at 6 months. The same protocol of an MSC-coated fistula plug implantation was then used to treat RVF fistulas. The plugs were implanted during EUA and were trimmed to the fistula diameter and length. At 3 months, symptom improvement was seen in 4 out of 5 (80%) patients with no adverse events or evidence of radiographic sepsis.[145]

Pouch Fistulas – Crohn's Disease of the Pouch

Restorative proctocolectomy (RPC) was first performed in 1977 at St Mark's Hospital and described by Sir Alan Parks and Professor John Nicholls in 1978. The RPC was developed for

the restoration of GI continuity in patients following proctocolectomy, with the primary aim of avoiding a permanent ileostomy.[149] RPC has been widely adopted and favored as the restorative procedure of choice for its acceptable safety profile and high patient satisfaction.[150,151] Fulminant or refractory ulcerative colitis (81%) and familial adenomatous polyposis syndrome (10%) are the most common indications for RPC.[152]

RPC has evolved over the last 4 decades. There has been a trend towards employing total mesorectal dissection over close rectal dissection for proctectomy, minimal access surgery for pouch construction, and trans-anal stapled anastomosis has also replaced a hand sewn anastomosis.[152] The ileal pouch reservoir can be created in 2 limb (J), 3 limb (S), 4 limb (W), or isoperistaltic (H) formations. Of these, the J- pouch has become the preferred technique due its relative ease and association with superior clinical outcomes. Adequate blood supply to the ileal pouch from branches of the superior mesenteric artery and a tension free pouch anal anastomosis are the core tenets for achieving a successful ileoanal anastomosis.[153] A defunctioning loop ileostomy is commonly fashioned to control complications of pelvic sepsis associated with an anastomotic leak at the ileal pouch anal anastomosis (IPAA).[154] A meta-analysis of 17 studies comprising 1486 patients found that the risk of pouch-related leak was significantly higher in the absence of a defunctioning ileostomy.[155] A randomized controlled study of 45 patients did not show any difference in anastomotic leakage or pelvic sepsis with or without defunctioning.[156] Due to conflicting evidence from mainly observational studies, it remains unclear whether defunctioning loop ileostomy reduces the risk of an anastomotic leak. However, as the morbidity of pelvic sepsis can be devastating, most centers advocate forgoing a defunctioning ileostomy in a highly selected group of patients.[157] An anastomotic leak from the pouch is associated with significant morbidity from the sequalae of chronic pelvic sepsis, collection, poor pouch function, and pouch fistulae.[158]

The 2017 Ileoanal Pouch Registry (IPR) reported a pelvic sepsis rate of 9.4%, of which pouch fistula was noted in 4.7% of the cohort, from data submitted by 80 UK and European centers of 5352 pouch operations over 4 decades.[152] Pouch fistulae are one of the main causes of pouch failure as described by pouch diversion and/or pouch excision.[151] The overall rate of pouch failure is reported as 10% of patients after RPC,[159] whereas pouch failure has been reported in up to 29% of patients with a pouch fistula.[160] However, pouch failure is a subjective outcome as it requires the surgeon and patient to choose defunctioning or excision. A true reflection of pouch failure should involve a patient reported quality of life measure, which is likely to report a higher rate of pouch failure. A quality of life measure will reveal a cohort of patients who are unsatisfied with their pouch function but may not be suitable candidates for further surgery or may find the alternative of a permanent ileostomy unacceptable. The high rate of pouch failure in pouch fistula is a reflection of the clinical challenge they pose to the surgeon.

We have recently described pouch fistula as related to anastomotic dehiscence, inflammatory disease, cryptoglandular disease, and malignancy.[161] Pouch fistula has also been classified according to the time of onset, as "early" or "late."[158] Early onset pouch fistulae manifest within 12 months from pouch creation and are more likely associated with an anastomotic leak, and may present following a reversal of the defunctioning ileostomy. Late onset pouch fistula are thought to be associated with a chronic inflammatory etiology such as CD.[153,160] However, a classification based purely on timing cannot incorporate non-inflammatory fistulae, nor the fistula that appears as a late complication following an earlier, perhaps subclinical anastomotic defect, nor does it address the question of cancer. In this section, we discuss in detail the etiology, presentation, assessment, and management of a pouch fistula.

Etiology

In the published literature to date, pouch fistulae of varying etiology are often conflated, confusing the reader and rendering void any attempt at analysis of interventions. In our experience, pouch fistulae can be classified according to etiology, into 4 distinct groups; anastomotic, inflammatory, cryptoglandular, and malignant. These groups have characteristic clinical presen-

tations, vary in morphology, and require different management strategies. Rare causes outside this etiological framework includes iatrogenic injury to the anal canal, pelvic radiotherapy, and rare infectious diseases. A standardized practice of etiological classification of pouch fistula will enable focused and effectual management, as well as measurement and comparison of clinical outcomes across institutions or techniques, in homogenous groups.

Classification

Group 1 Anastomotic Dehiscence and Pelvic Sepsis

Pouch fistulae that originate from an anastomotic leak can manifest with chronic pelvic sepsis and pouch dysfunction. They are often identified within 12 months of pouch construction or ileostomy reversal, and the timing of the fistula is usually, but not always, early. The internal opening of the fistula is identified at the ileoanal anastomosis, and may end with an external opening in the perineum or perianal skin. They may involve multiple tracts, and be related to a peri-pouch or presacral collection. They may fistulate into surrounding visceral structures including bladder, prostate, urethra, and vagina.[160] This group of fistulas may also originate from an anastomotic dehiscence at the pouch body, or pouch apex, ending as an external opening at the abdominal wall or developing a cavity with a collection.[162]

An anastomotic leak at the pouch that develops into a blind ending tract resulting in a collection in the presacral space, or peritoneal cavity is defined as a pouch sinus. In the absence of an anastomotic leak, a diagnosis of IBD such as CD should be considered[10], but the leak itself may be hard to identify and such a cavity running from the anastomosis is most likely to represent an anastomotic leak. An increased risk of an anastomotic leak and pouch fistula formation is associated with technical factors arising from intraoperative challenges in constructing the IPAA. Patient factors such as poor nutritional status, immunocompromise due to preoperative steroids, and obesity is more common amongst the early pouch fistula group.[160,163] The role of biologics in pelvic sepsis has also been discussed. A nationwide cohort study from Denmark which included 1456 patients with an RPC between 1996 and 2013 reported an increasing incidence of pelvic sepsis, from 2.5 % in 1996 to 9.6% in 2013. The authors hypothesized that increasing patient age, comorbidities, and the increasing use of biologics may explain the increase in incidence of pelvic sepsis.[157] The authors referred to a study from New York state which found that postoperative complications in patients with ulcerative colitis were higher in the era of biologics.[112] An increase in the incidence of pelvic sepsis in IPAA may be due to the self-selection of more severe cases of ulcerative colitis which have failed to respond to biologics.

Pouch vaginal fistulas can be caused by iatrogenic injury to the vaginal wall during proctectomy, or through unwittingly incorporating the vagina when firing the stapler for construction of the ileoanal anastomosis.[153] Pouch vaginal fistulas occur in 6.3% of female patients with an IPAA, and are very difficult to manage.[162] Late onset pouch fistulas may sometimes arise from a subclinical anastomotic leak which develops into a fistula over time.[158]

Group 2 Crohn's and Inflammatory disease

Pouch fistulae caused by inflammatory disease may have characteristic clinical and histological features of CD. However, some may fall anywhere along the spectrum of an underlying etiology that may be suggestive of indeterminate colitis, indeterminate colitis favoring CD, or a persistent inflammatory process that is yet to be established. These fistulae may arise from the pouch, cuff, dentate line, or the anastomosis.[158] Here, we classify these fistulae into 2 subgroups.

Group 2a Crohn's Disease Related

A primary diagnosis of ulcerative colitis may need to be revised to CD in the presence of a new pouch fistula and signs indicative of CD. CD has been found to be more common in late onset fistulae.[160] Patients should be assessed for perianal features of CD as well as luminal disease such as small bowel strictures or discontinuous small bowel disease on enterography. The

presence of anal tags, fissures, anal stenosis, multiple abscesses, and complex fistulous disease should increase the index of suspicion for CD.

A 30-year follow-up of IPAA at the Mayo Clinic found a higher cumulative probability of pouch fistulae in patients with CD (68%) compared to ulcerative colitis (14%), with a pouch excision rate approaching almost 50% in those with CD.[151] These fistulae are more likely to respond to TNF- α.[160]

Group 2b Inflammatory Disease Related

Pouch fistulae that do not demonstrate any features of CD such as necrotizing granulomas on histology, are thought to be inflammatory in nature and deserve to be viewed as a separate entity. Histology is likely to show features of chronic inflammation. Cuffitis, pouchitis, and prepouch stricturing are not diagnostic of CD, but fistulae arising in an inflamed pouch or cuff may still be managed as inflammatory disease. The management of these fistulae differ from anastomotic fistulae. Group 2 pouch fistulae are managed similarly to non-pouch CD related fistulae with medical treatment predominating with limited surgical options.

Group 3 Cryptoglandular Related

Cryptoglandular fistula disease in the healthy population manifests at a rate of 1-2 per 10000. Fistulae arising at the dentate line in patients with pouches without an anastomotic or inflammatory cause occur at a higher rate. In the non-pouch cohort, CD, and, to a lesser extent, ulcerative colitis, there is increased risk of a persistent fistula following perianal abscess.[164] The factors driving fistula formation and persistence seem amplified in the presence of IBD and also in pouches, even in the absence of luminal inflammation. These factors are poorly understood but urgently sought.

Group 4 Malignancy Related

Although pouch fistulae arising from a primary malignancy are rare, they are associated with significant morbidity and very poor prognosis. A high degree of clinical suspicion should be adopted for patients with any new onset, late pouch fistula, a background of familial adenomatous polyposis (FAP) syndrome, or dysplasia or malignancy in the presence of ulcerative colitis, and those who have not participated in regular pouch surveillance, despite these features.[10]

The absence of common etiological factors such an anastomotic dehiscence or IBD should raise concern. Meticulous investigation to rule out malignancy should include pouchosocopy, EUA with biopsy, and pelvic imaging. Malignancy related pouch fistulae should be managed by a multidisciplinary team, in a specialist center as pelvic exenteration is often required.

As well as defining the etiological basis of pouch fistula, a detailed understanding of the anatomical location of the fistula in relation to the anal canal, pouch, and visceral structures is crucial for planning further management. Local and luminal Imaging, pouchosocopy, EUA, and the use of video-assisted techniques may be useful in anatomical classification and luminal assessment.

Pouch fistulae can be described in relation to the ileoanal anastomosis as above, below, or at the anastomosis or in relation to the dentate line. They may also arise from the pouch body, either the efferent or afferent seams of the pouch, or the apex of the J-pouch. They may fistulate into the perineum, perianal region, and visceral structures.[153,160] The clinical manifestation of these fistulae may provide clues to their origin and associations.

Clinical Manifestation

Pouch fistulae may present with a change in pouch function involving increased frequency, nocturnal seepage, urgency, and pelvic discomfort. General malaise, low grade pyrexia, and malnutrition will feature in coexisting chronic pelvic sepsis.[158]

Pouch vaginal fistulae may be asymptomatic but often manifest with discharge of flatus, feces, or mucous through the vagina. This may cause dyspareunia, vaginal irritation, and recurrent

vaginitis. Fecal discharge per vagina will also lead to excoriation and irritation of the perineum.[5] Pouch cutaneous fistulae will manifest with mucous discharge and may also be associated with pelvic discomfort. Marked perineal excoriation can be found in the presence of seepage, incontinence, and discharge and features of perianal CD's such as anal tags, strictures, and fissures may co-exist. Co-existent pouchitis, pouch dysfunction, and luminal CD will also influence the management and should be identified.

In significant fistulous disease, patients will note a change in their quality of life including ability to continue with daily activities, employment, and intimate social relationships. These parameters are useful to document, as they will help guide management, assess outcome, and, in cases of progressive symptomatology or failure of conservative management, may aid in decision making for pouch diversion or pouch excision.

Diagnosis and Investigations

The diagnostic assessment should center around 3 questions: What is the etiology of the fistula? What is the anatomy of the fistula? Is there evidence of luminal or other perianal disease? A combination of pelvic MRI, pouchosocopy, and EUA will help answer most of these, with luminal imaging also sometimes necessary.

Features of IBD such as luminal inflammation, stenosis, or fistula, and acute inflammation of the pouch inlet or pre-pouch ileum should be assessed on pouchosocopy or by EUA and confirmed on biopsy. Understanding the relationship of the fistula to the dentate line and the anastomosis is crucial. The presence of ileal (cuff or pouch) inflammation or distant luminal disease can be assessed on a combination of pouchosocopy and CT/MRI enterography. Evidence of malignancy should be sought at EUA and histologically. Pelvic MRI will be also be helpful for the assessment of peri pouch collection, cavity, or intraperitoneal extension of a pouch fistula.[158]

Medical Therapy

Studies reporting on how best to medically treat CD of the pouch are lacking. There are no published randomized controlled trials, and treatment recommendations are largely based on subjective experience from large volume IBD centers.

Similar to the treatment of CD in nonpouch patients, medical therapy for patients with fistulizing CD of the pouch is formulated with either maintenance or remission in mind. Pharmaceutical agents like antibiotics, immunomodulators, and biologic agents (anti-TNF/anti-integrin) are routinely used with varying success noted in the literature. Favorable response to these medical therapies have been anecdotally associated with the following factors: simple fistula with a short tract; a nonobese, nonsmoking patient; contemporaneous pouch inflammation near fistula opening and; lack of distal pouch/anal stricture.[165]

Antibiotics

Although oral antibiotics such as ciprofloxacin and flagyl are a common first-line treatment for pouchitis, the therapeutic benefit in CD-related pouch fistulae are largely unknown. They may be helpful in relieving symptoms related to pouch inflammation but commonly do not result in significant mucosal changes seen on endoscopy. Since patients with CD-related pouch fistulae are thought to carry a higher incidence of small intestinal bacterial overgrowth (SIBO), an unstudied benefit of antibiotics may be due to treatment of concomitant SIBO. Long-term oral antibiotic use in these fistula patients may be augmented by simultaneous administration of immunomodulatory or biologic therapy for added clinical benefit.[165]

Aminosalicylate (ASA) Derivatives

Topical and/or oral mesalamine has not been formally studied in the treatment of CD of the pouch, but may be administered in topical (enema or suppository form) as induction therapy or to achieve remission for inflammatory CD of the pouch/pouchitis. Its primary use for fistulizing pouch disease is limited, as it may help only by reducing inflammatory symptoms when fistulae occur in the setting of inflammatory CD.[166]

Corticosteroids

Similar to ASA-derivatives, corticosteroids are primarily valuable in the treatment of inflammatory CD of the pouch. Budesonide, in either oral or topical form, and prednisone (or IV methylprednisolone) are effective combatants of CD-related inflammation, but derivatives of prednisone should be limited to induction therapy without long-term use. There is limited understanding of utility in CD-related pouch fistulae.[167,168] Intralesional injection of longer-acting steroids such as kenalog, although helpful for fibrotic strictures, has a limited role in treating CD-related pouch fistulae.

Immunomodulators

The use of immunomodulators (IM) such as 6-mercaptopurine (6-MP), azathioprine (AZA), and methotrexate (MTX), as monotherapy or combination therapy with IFX, has been reported in case reports and a small case series as a possible treatment strategy for CD of the pouch.[169,170] There is very limited evidence describing success of use with CD-related pouch fistulae, and long-term efficacy and safety of IM in these patients warrant further investigation. Although inflammatory CD of the pouch may benefit from monotherapy with IM, those with fistulizing disease may require the addition of biologic therapy for best outcomes.[165]

Biologic Agents

Anti-TNF biologic agents such as IFX and adalimumab (ADA) have shown promise in the treatment of CD of the pouch, and appear to be effective specifically in the setting of fistulizing disease in these patients, although large studies are lacking. One case series from the Mayo Clinic describing 26 fistulizing pouch patients reported 62% of patients with complete short-term response to IFX, and 23% of the group showed partial response (median follow-up 22 months). Of these responders, 67% maintained acceptable function of the pouch.[171] Another retrospective study of 15 patients with CD fistulae of the pouch described outcomes after managing these patients with anti-TNF in combination with other intervention (eg, setons, collagen plug insertion, and flap repair). They reported an overall healing rate of 53% for those CD-related pouch fistula.[108] Other smaller studies reported similar responses to IFX therapy[172] (Table 5).

Monitoring of Medical Therapy

The disease course and treatment response of patients undergoing care for CD of the pouch should be monitored closely. Most providers follow a "treat to target" surveillance approach, despite no real consensus with regard to the "target." For fistulizing disease of the pouch, clinical monitoring may be augmented by periodic EUA and pelvic MRI to check healing, but patient symptoms and quality of life should be weighted heavily.[165]

Table 5
Treatment studies of Crohn's disease of the pouch: medical therapy.

Authors	N	Study Design	Phenotype	Medical therapy	Primary outcome	Findings
Colombel[171]	26	Retrospective	Fistulizing fibrostenotic inflammatory	IFX	Clinical response	62% complete response 23% partial response 15% no response
Mallick[173]	36	Retrospective	Fistulizing	Surgery + Medical therapy	Fistula healing	53% pouch failure, fistula healed in 3/6 with combined med/surg therapy
Gaertner[108]	15	Retrospective	Fistulizing	IFX + Surgery	Pouch failure/fistula healing	53% healed fistula
Li[174]	48	Retrospective	Fistulizing fibrostenotic inflammatory	ADA	Clinical/endoscopic response	50% complete response 21% partial response 29% no response (after induction)
Haveran[170]	22	Retrospective	Fistulizing fibrostenotic inflammatory	AZA/6MP +/-IFX	Pouch failure/improved frequency	46% pouch failure, slight improved frequency in treated group

ADA, adalimumab; IFX, infliximab; 6MP, mercaptopurine.

Operative Intervention

Surgical therapies for fistulizing CD of the pouch may be employed independently or in combination with medical and endoscopic treatments. Regardless of strategy, it is most important to consider the desires of the individual patient, and his or her personal definition of quality of life, as this should be the ultimate measure of treatment effectiveness. Many patients diagnosed with CD of the pouch desire pouch preservation and should be offered an evaluation for such in a high volume IBD center with surgeons experienced in treating this challenging situation. Those who are not interested in pouch preservation and choose to pursue a permanent conventional ileostomy should be equally supported in this endeavor as well. In either case, the majority of patients with fistulizing CD of the pouch benefit from both medical and surgical therapy in parallel.

A patient with a diagnosis of CD of the pouch does not necessarily condemn him/her to pouch removal with permanent conventional ileostomy. Disease phenotype heavily influences the degree of pouch retention. A study of 65 patients with de novo CD of the pouch reported that 57% were able to maintain their pouch with acceptable function despite this diagnosis, with the appropriate combination of medical, endoscopic, and surgical strategy. However, this multivariate analysis noted that the presence of fistulae at the time of diagnosis of CD of the pouch, along with early diagnosis, were independent risk factors for pouch failure.[175]

Diagnosis With Exam Under Anesthesia

The foundation for treating fistulizing CD of the pouch is making an accurate assessment of a very challenging situation. An EUA is often the best first operative option in these patients, allowing the surgeon to both establish the correct diagnosis and to provide therapeutic benefit with sepsis control or biopsy. Fistulae from pouch CD is easily confused with pelvic sepsis from a chronic pouch anal anastomotic leak, and distinguishing between these is critical as the

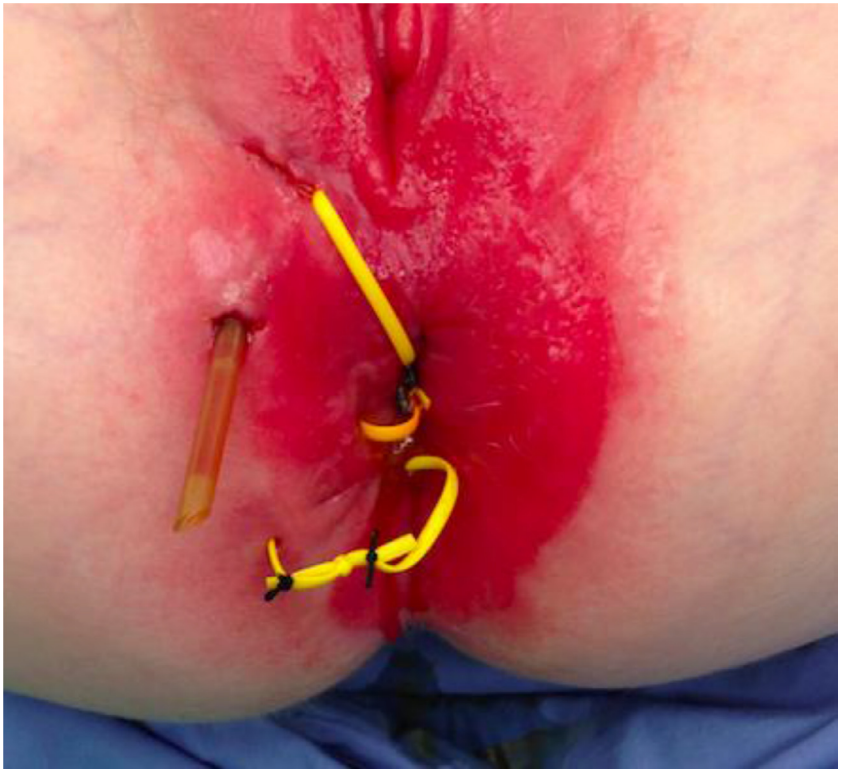

Fig. 4. Anoperineum in a patient with CD-associated fistulizing disease of pelvic pouch. Both mushroom and seton drains are utilized for control of sepsis.

treatments are vastly different. It is generally accepted that a diagnosis of pelvic sepsis within 3-6 months following ileostomy closure after IPAA is likely a postoperative complication rather than a sequela of CD of the pouch, which is more likely to manifest more than 12 months after IPAA.[176,177] An EUA allows for a thorough examination without patient discomfort, and simultaneous pouchoscopy/biopsy with assessment of the remaining pouch to identify other sequelae of CD that may help with diagnosis.

Control of Sepsis

An initial EUA allows the surgeon to carry out the next critical step of managing CD-related pouch fistulae, which is control of sepsis. This can be performed using carefully placed mushroom drains in abscess cavities and noncutting silastic setons to manage fistula tracts that are present (Fig 4). Indiscriminate injury or division to the anal sphincter complex should be avoided, as the risk for fecal incontinence is high. Cautious and gentle completion of these local procedures controls symptoms, improves quality of life, and helps to maintain the best chance for pouch preservation for the future.[178]

Fecal Diversion

A diverting loop ileostomy with pouch in situ is an effective method of controlling symptoms from fistulizing CD of the pouch when the patient has failed medical/endoscopic therapy and/or

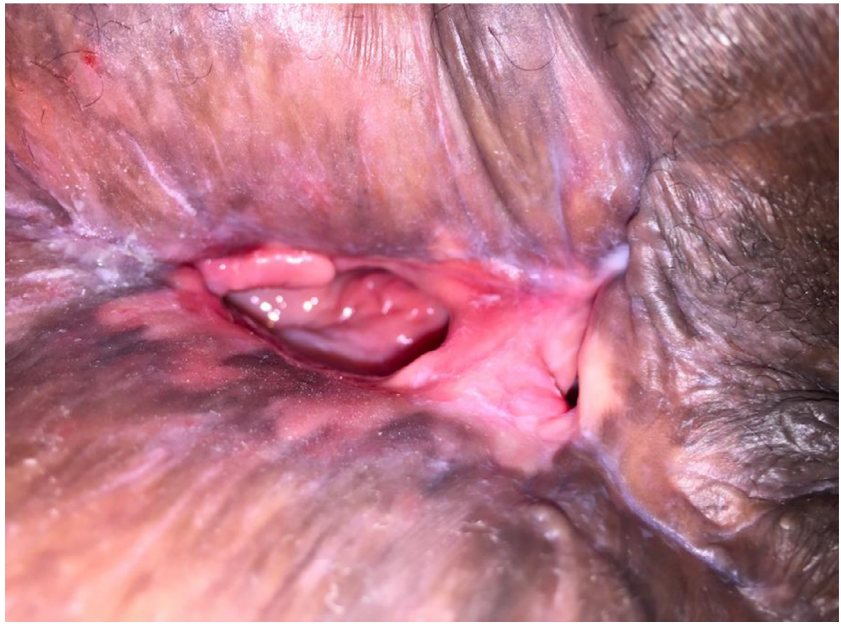

Fig. 5. Non-healing perineal wound after pouch excision in setting of fistulizing CD of the pouch. This unfortunate patient also developed a persistent connection between her vagina and perineal wound, resulting in significant morbidity.

is not ready to commit to pouch excision or pouch revision (if an option). This allows for better control of anoperineal sepsis (in combination with the above local procedures) and improvement of quality of life. It also is a helpful "first step" if pouch excision or pouch revision is chosen, as the pouch and anoperineum are cleared of active sepsis, and the patient regains his/her health, nutrition, and mental fortitude in preparation for next steps. It is important to emphasize that fecal diversion improves but does not necessarily resolve anorectal symptoms, as patients may experience ongoing mucous drainage and untoward symptoms from diversion pouchitis.[177]

Pouch Excision

Pouch excision is an effective surgical option when medical, endoscopic, and local surgical therapies fail, but does come with the risk of high morbidity. Pathologic confirmation of CD of the pouch is not always confirmed after pouch excision, as shown in a series of 35 such patients, with only 7 cases achieving pathologic diagnosis of CD[14]. A dreaded complication of pouch excision is the non-healing perineal wound with development of perineal sinus, which can be more difficult to manage than a pouch in situ. This occurs in up to 40% of patients and the risk for this morbid complication should be considered when developing a surgical strategy[179] (Fig 5). Initial fecal diversion with staged pouch excision may help reduce the risk for nonhealing.

Pouch Revision

Highly selected, motivated patients suffering from fistulizing CD of the pouch may be candidates for pouch revision, either with perineal/perianal repair of the existing pouch or major revisionary pouch surgery with recreation of a new pouch-anal anastomosis and/or pelvic pouch.

Any surgical repair of a pouch fistula requires initial sepsis drainage to normalize tissue quality, coupled with medical CD therapy to reduce inflammation and promote healing of tissues prior to surgical repair. During this time, response to therapy is monitored and assessed, and discussions regarding next steps of surgical care must establish reasonable patient expectations and goals of surgery in these very challenging cases.

Local procedures such as seton placement, mucosal advancement, and fistulotomy have been studied as a means to mitigate symptoms of CD-related pouch fistulas. Although there is evidence to support the use of local procedures for CD-related pathology of the pouch, the presence of a fistula at the time of CD diagnosis was an independent risk factor associated with pouch failure.[175]

Data regarding intentional pouch revision for CD pathology of the pouch are very limited. Unpublished data regarding patients undergoing intentional redo IPAA for pouch CD revealed pouch retention rates were lower than index pouches (<60% vs 79% at 5 years), but perioperative complications and functional outcomes were comparable. This emphasizes the extreme importance of careful patient selection in the pouch CD population. Additionally, revisionary IPAA surgery for CD of the pouch has shown acceptable outcomes of this strategy in very selected patients who present for surgery with no active anoperineal disease, limited small bowel disease, and an uncompromised anal sphincter.[180] Above all, any patient undergoing pouch revision for fistulizing CD must be insightful to the complexity and limitations of redo surgery in this setting, and must be highly motivated and passionate to pursue this option. They must accept the increased risk for postoperative complications, higher risk for eventual pouch loss, and need for postoperative long-term medical therapy.

When considering surgical options for fistulizing CD of the pouch, it is important to reemphasize that many patients are referred to pouch centers with a diagnosis of pouch failure due to CD, when failure is actually due to technical complications at the pouch-anal anastomosis and resultant anoperineal sepsis. These patients are commonly good candidates for a redo pouch but were never considered for such due to an incorrect diagnosis of CD.[176] It is critical to make as accurate a diagnosis as possible for best outcomes for this challenging patient population.

Conversion to Continent Ileostomy

A continent ileostomy (CI) has traditionally been offered to only those highly motivated patients who require proctocolectomy but are not candidates for or who fail restorative pelvic pouch surgery (ie, unusable anal sphincter or pelvic floor dysfunction).[181] For those who suffer from CD-associated pouch failure, CI may be an alternative to permanent conventional ileostomy, albeit with the possibility of certain limitations. The largest study regarding CI creation in CD patients showed that the pouch failure rate, regardless of whether a diagnosis was made pre-CI or post-CI creation, was 46%, with major surgical revision required in 83% of patients in the study.[182] The offering of CI in patients with CD-related pouch failure must be thoughtful and always requires a knowledgeable, well-informed and extremely motivated patient with a desire to avoid conventional ileostomy, along with the physical and mental fortitude required for this commitment.

Concluding Remarks

Treatment of CD-associated pouch fistulae require a multidisciplinary, multidimensional approach with the goal of treatment centered upon maximizing the patient's quality of life. It is imperative to create a patient-specific strategy including elements of both medical and surgical therapies for optimal outcomes. When patients who are facing CD-related pouch failure and are very motivated to avoid a conventional permanent ileostomy, revisionary pouch surgery may be feasible and successful in selected cases.

Enterocutaneous Fistulas Complicating Crohn's Disease

Enterocutaneous fistulas (ECFs) represent abnormal communications between the GI tract and skin and represent only 5.6% of the fistulas developing in patients with CD.[88] Although ECFs may result from surgery, they more commonly occur as a consequence of underlying bowel inflammation.[183,184] Disease-related fistulas infrequently resolve with medical therapy,[183] and the majority of affected patients require operative intervention with bowel resection.[185] Moreover, these ECFs are commonly accompanied by malnutrition as a consequence of coexisting sepsis, concomitant abdominal infection, and high fistula output,[184,186] and the warranted operations can be associated with relatively long hospital stays and higher rates of morbidity and mortality.[186]

Symptoms, Signs, and Presentation

ECFs can present in manifest healthy patients as their initial sign of CD or patients with several years of active disease. The fistulas can spontaneously occur or develop following a procedure such as percutaneous abscess drainage or intestinal resection.

The classic clinical finding is an external fistula opening located on the anterior or lateral abdominal wall that is commonly surrounded by erythematous, indurated, and tender skin. The opening can be obvious or hidden beneath a skin fold, involve a previously undisturbed area of skin or old scar, or lie at the site of a recent or open procedure-related incision. The discharge can be intermittent or continuous, and purulent or fecal. Lastly, the output can be categorized and quantified as low ($<$200 mL/day), moderate, or high ($>$500 mL/day).

Post-procedural ECFs can manifest early (within 7 days of procedure) with a combination of fever, hypotension, tachycardia, ileus, diffuse or localized abdominal tenderness, respiratory distress, acidosis, elevated C-reactive protein, and leukocytosis. Alternatively, ECFs may manifest late (greater than 7 days after procedure) during a prolonged hospitalization or following discharge as an erythematous, fluctuant, or tender area at a former drain site, laparoscopic port site, or surgical incision, with or without the above-mentioned signs.

Diagnostics/Imaging

Initial laboratory testing should generally include myriad assays intended to assess indicators of dehydration, electrolyte/metabolite imbalances, infection/sepsis, and malnutrition. Once the patient has been stabilized, imaging studies should be obtained.

Fistulography was historically the principal modality used to investigate ECFs and remains a useful complementary technique to confirm communication between the skin orifice and instigating segment of the GI tract, but debris, edema, or extrinsic compression impeding contrast medium flow into the intestinal lumen can produce false negative studies. The external opening is cannulated with any number of devices (eg, pediatric/standard nasogastric tube, urethral catheter, venous cannula) depending on its diameter and low-osmolar water-soluble iodinated contrast medium is injected with minimal or no pressure under fluoroscopic observation. Fistulography directly visualizes the involved small or large bowel segment and provides valuable information about the ECFs anatomy such as caliber, course, and length of the tract, but CT or MRI is employed as an adjunct to obtain useful information about mural and extraluminal abnormalities affecting the culprit and neighboring intestine (Fig 6).

Most patients should undergo CT or MR studies to obtain cross-sectional information about the ECF and the underlying CD. Multidetector CT is preferred in severely ill or uncooperative patients because it limits motion or peristalsis artefacts by quickly acquiring high-spatial resolution. In the setting of an ECF, intravenous contrast medium is generally warranted unless contraindicated and orally administered contrast medium opacification may be helpful to ease

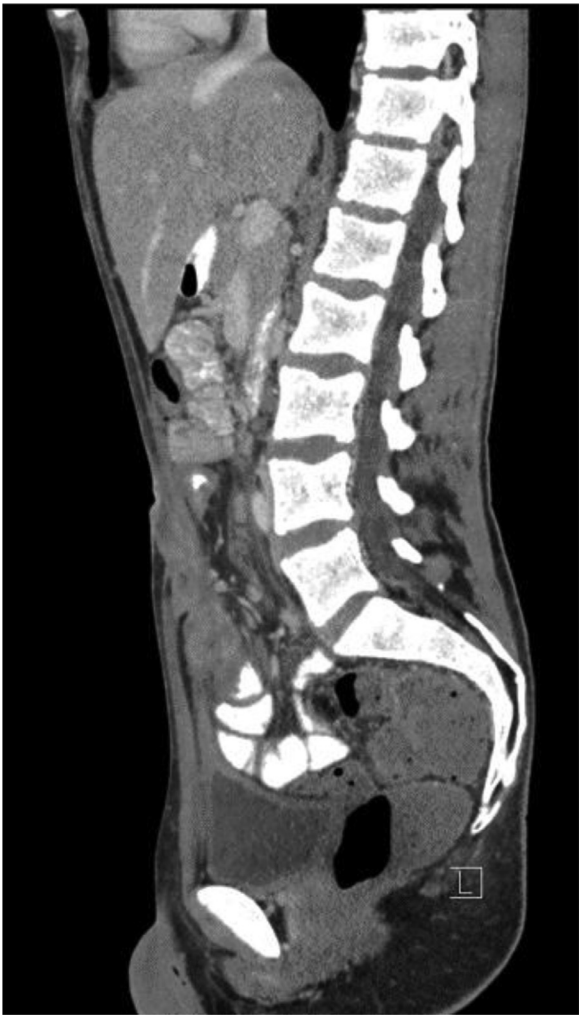

Fig. 6. CT image of enterocutaneous fistula secondary to Crohn's disease of the terminal ileum.

differentiation of bowel loops from extraluminal structures and abnormal collections in patients with scarce intra-abdominal fat.

Alternatively, CT-fistulography with prior injection of iodinated contrast medium (eg, 3% diluted iopamidol or iohexol) into the external opening is a useful technique that combines cross-sectional imaging with opacification of the involved intestine. Image reconstruction and study interpretation along the sagittal plane are recommended because this approach provides the best visualization of the anterior abdominal wall.

The usual CT appearance of an ECF includes a tubular structure originating from a bowel loop that passes in a ventral or ventro-lateral orientation through the peritoneum and courses through muscles and fascia layers of the abdominal wall to reach the skin surface. ECFs can appear either collapsed or patent with gaseous or fluid content. The latter scenario creates the characteristic "tram-track" appearance.[187] Fistula walls can be of varying thickness, but peripherally enhancing cavities containing fluid or gas may represent an abscess arising along the tract.

Any associated abscess should be drained percutaneously when possible in order to reduce the likelihood of operative complications or improve the chance of spontaneous closure.

Postoperative ECFs in cachectic patients with very thin subcutaneous and muscular planes of the ventral abdomen may show the involved bowel loops converging towards the ECF site and closely adherent to the peritoneal serosa. The external opening generally corresponds to a focal cutaneous retraction or depression and is often surrounded by thickened inflamed skin. Alternatively, a frank cutaneous breach or discontinuity may be seen, especially in instances of high output ECFs.

MRI has intrinsically superior soft tissue contrast compared to CT and may better define the fistula tract, but the former modality is hampered by respiratory and peristaltic artifacts from bowel obstruction or ascites. In patients who can sufficiently cooperate, MRI protocols to investigate ECFs should rely on multiplanar fluid-sensitive T2-weighted images including the anterior abdominal wall. Additionally, intravenous administration of gadolinium contrast medium is helpful to visualize hypervascular ECF walls, abscess collections, and surrounding fat planes.

On heavily T2-weighted MR sequences, the ECF appears as a fluid-filled hyperintense tubular structure traversing the abdominal wall and subcutaneous fat to reach the skin surface. The fistula walls demonstrate variable, generally intermediate signal intensity on both T1- and T2-weighted acquisitions, with corresponding "tram-track" enhancement on post-gadolinium images. Over time, persistent ECFs tend to develop thicker walls with lower T2-weighted signal secondary to fibrosis and decreasing intensity of contrast enhancement. The presence or absence of bowel communication is generally more challenging to detect with MRI compared to CT.[187]

Universal Approach

ECFs arising in patients with CD are best managed by a multidisciplinary approach that requires a team of individuals including the surgeon, gastroenterologist, infectious disease specialist, interventional radiologist, nutritionist, and wound/ostomy nurse, as well as a dedicated ancillary unit comprised of specialized nurses, pharmacists, dieticians, and case management/social workers. Several basic tenets of ECF management exist (Table 6) and they should be generally employed regardless of the presentation Table 6.

Medical Management

As previously mentioned, ECFs may occur as a primary manifestation of CD, especially after abscess drainage, but nearly 25% arise secondary to anastomotic failure after intestinal resection.[104,188] In addition to employing the above-described measures, the etiology of the fistula must be sought because the cause often dictates the optimal management. Regardless, corticosteroids are rarely legitimized in this setting and it is imperative that all infection is addressed before disease-focused medical therapy is initiated.

Patients who develop an ECF after drainage of an intra-abdominal abscess will usually require operative intervention because their intestinal disease in this scenario is rarely suited to medical therapy alone. Moreover, they are often candidates for postoperative disease prophylaxis with a biologic agent and it is likely better to withhold usage of these medications in the preoperative period so they can be prescribed in a naïve postoperative patient.

Conversely, a non-operative approach is best suited for a low output fistula that arises late after an intestinal resection where no residual disease remains, and any associated sepsis has been well controlled. In these instances, bowel rest and nutritional support usually allow spontaneous closure of the fistula given an appropriate duration of therapy. Treatment with biologic agents is typically unwarranted in this setting because the fistula has likely resulted as a surgical complication rather than a disease manifestation. Successful closure has been anecdotally reported in 3 patients who developed late ECFs from their anastomoses and were managed with an antitumor necrosis factor (TNF) agent after endoscopy showed active disease involving the anastomosis.[189]

Table 6
Basic tenets of enterocutaneous fistula treatment.

Treatment tenet	Comment
Control sepsis	Broad-spectrum antimicrobial therapy
	Drainage (e.g., image-guided) of associated abscess
Limit fistula output	Initial bowel rest
	Proton pump inhibitors
	Consider octreotide administration
Optimize metabolic and nutritional parameters	Correct electrolyte and fluid imbalances
	Initiate elemental or parenteral nutrition
Protect the skin	Employ dry gauze dressing or pouching appliance
	Consider negative pressure dressing
Assess likelihood of spontaneous closure	Spontaneous fistula
	Active infection/inflammation
	Distal obstruction
	History of radiation
	Length of tract
	Size of enteric defect
	Postprocedure fistula
	Active infection/inflammation
	Distal obstruction
	Foreign body
	History of radiation
	Length of tract
	Size of anastomotic defect

An audit from an intestinal failure unit in the United Kingdom reported that loss of small intestine length due to repeated bowel resections was the cause of intestinal failure in less than one quarter of patients with intestinal failure and CD.[190] Instead, the majority (61%) of patients with CD who developed intestinal failure did so because of abdominal sepsis in the early postoperative period. Patients in this latter group typically underwent multiple laparotomies over a relatively short frame time after the initial operation and this led to short bowel or ECFs. Accordingly, a conservative approach that leverages nonoperative measures should be adopted when dealing with postoperative ECFs following intestinal resection for CD. Endoscopic and percutaneous methods of ECF closure in these cases have been described and may be considered at institutions where the appropriate technical expertise is available.[191,192]

For primary ECFs complicating CD, medical treatment may be attempted, but the evidence for such an approach is minimal and of low quality. A recent review of all the randomized controlled trials targeting patients afflicted with fistulizing CD revealed the vast majority of studied patients suffered from anoperineal fistulas and it was difficult to tease the results of patients with ECFs from all the others.[193] Furthermore, of the 27 trials, only 3 employed objective cross-sectional imaging modalities for disease assessment and most studies relied on physical examination and physician/patient-reported observations for assessment of outcomes.

Amiot and colleagues retrospectively reviewed the outcomes of CD patients with ECFs (excluding anoperineal fistulas) treated with anti-TNF agents followed in the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID) centers.[194] Of the 48 patients followed a median of 3.0 years, ECFs arose from the small bowel (n = 38), duodenum (n = 1), and colon (n = 9); the fistulas developed from an ileocolic anastomosis in 17 (35%) cases. An abdominal abscess developed in 15 (31%) patients and complete ECF closure occurred in 16 (33%) patients, of whom 8 relapsed during the follow-up period. In multivariate analysis, complete ECF closure was associated with the absence of multiple ECF tracts and lack of distal intestinal stenosis. Operative resection was required in 26 (54%) patients, and the only mortality in the entire cohort occurred secondary to abdominal sepsis after surgery. The investigators concluded that anti-TNF therapy may be effective in selected patients, especially in the absence of a complex fistula and concomitant distal stenosis.

Parsi and colleagues similarly found complete closure of an ECF or complete cessation of ECF drainage occurred in 3 of 8 (38%) patients with ECFs who were followed at least 3 months after 3 IFX infusions; 2 additional patients experienced a partial response.[103]

Fistula healing in the subgroup of patients with anoperineal or ECFs at baseline (n = 117) was a secondary endpoint of the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) double-blind, placebo-controlled, randomized trial.[195] Post-hoc analysis that specifically focused on the efficacy of adalimumab over time in this subgroup confirmed the superiority of adalimumab over placebo for fistula healing after 56 weeks. Data from CHARM combined with data from the open-label extension study, Additional Long-Term Dosing with Humira to Evaluate Sustained Remission and Efficacy in CD (ADHERE), showed no significant increase in serious adverse events for patients treated with adalimumab.[196] Unfortunately, the results for patients specifically treated for an ECF could not be discerned from the studies. An anecdotal report has further suggested adalimumab may curtail symptoms associated with an ECF complicating CD.[197] A separate case report described the efficacy of ustekinumab in closing a CD-related ECF that was refractory to anti-TNF agent therapy.[198]

Yan and colleagues prescribed elemental nutrition for 48 patients with ECFs complicating their CD and reported that 30 (63%) patients experienced successful closure of their fistula after 3 months of therapy with an average closure time of 32 days.[199] Although the measured inflammatory parameters (ie, C-reactive protein, erythrocyte sedimentation rate, platelet count) improved in all enrolled patients, logistic regression analysis showed that a lower C-reactive protein level and an elevated body-mass index predicted a greater likelihood of beneficial response to elemental nutrition.

Operative Therapy

The timing of operation is dictated by the clinical scenario, but a semielective approach can often be utilized. A patient with active disease and malnutrition usually gains little benefit from more than 7-10 days of hyperalimentation, whereas advocates of an elemental diet will typically recommend longer intervals of intervention. In many instances, the local sepsis can be appropriately controlled, and associated parameters can be adequately normalized within 1 week of initiating parenteral antibiotics and draining abscess cavities of suitable size. During this optimization time, all necessary imaging and endoscopy studies are completed, and prior operative notes are reviewed to aid in planning of the surgery.

In a patient with an ECF manifesting as a primary manifestation of his/her CD or developing after intra-abdominal abscess drainage, a minimally invasive approach can often be employed safely in the elective setting, but the patient must be cautioned that the technique is associated with longer operative times and higher conversion rates than normal.[200] Preoperative planning for fecal diversion is also imperative, especially if the patient is at high risk for anastomotic breakdown secondary to high-dose corticosteroids, poor nutrition, or undrained sepsis or if he/she would not tolerate a septic complication because of significant comorbidities. In these instances, preoperative stoma site marking in 1 or more quadrants is warranted. Some surgeons like to use ureteral stents placed at the time of surgery to help identify the ureters especially when significant retroperitoneal inflammation is anticipated.

Although the above-described studies and documents help plan the procedure, it is not uncommon for the surgeon to encounter different or additional disease-related abnormalities that must be addressed once the operation is underway. Early in the operation, it is important to assess the amount of normal small bowel that is present and whether conversion is likely; a minimally invasive approach may be continued as long as the surgeon feels steady progress can be made.

It is generally most helpful to initially separate the abdominal structures from the anterior abdominal wall except at the fistula site. It might be best to delay disconnection of the fistula at this juncture to avoid spillage of enteric contents during the duration of the operation. However, in some cases, it is better to liberate the bowel and control the defect with clips, staplers, or

sutures. Regardless, any adhesed omentum is then detached from the bowel and the midgut is separated from the hindgut. The diseased bowel and its mesentery can then be addressed as per the surgeon's preference. It is important to consider that non-diseased bowel can be involved in the inflammatory process and must be spared, division of the mesentery can be difficult and lead to large dissecting hematomas, resection margins should be limited (<2 cm), and asymptomatic diseased bowel can be ignored. It is generally better to convert to an open procedure than compromise these principles. Any remaining inflammatory rind should be debrided to minimize residual biofilm and suction drainage employed as needed.

The decision to construct an anastomosis, create a diverted anastomosis, or avoid an anastomosis altogether is based upon many of the details earlier discussed as well as the duration of the operation and encountered blood loss.

In a patient with an ECF developing from a prior anastomotic leak that fails to resolve with nonoperative measures, operative intervention is usually best delayed until at least 6 months has passed since the last surgery. This interval allows the patient to return to an acceptable state of health and permits the adhesions to diminish so the risk for iatrogenic enterotomy at the time of reoperation is likely lessened. An open operation through a midline incision is generally warranted in this scenario and the fistula is best managed by resection rather than suture closure.[201] Otherwise, the procedure is conducted as previously described.

If ongoing sepsis from an anastomotic leak cannot be controlled by non-operative measures and earlier surgery is mandated, it is prudent to enter the abdomen away from the ECF site and limit the reoperation to creation of a proximal diverting loop stoma if a hostile abdomen is encountered. A more definitive procedure can be planned several months later when the situation has improved.

Conclusion

ECFs may occur in patients with CD as a primary manifestation, following percutaneous drainage of an intra-abdominal abscess, or after intestinal resection. Regardless, these fistulas require aggressive early treatment by a multidisciplinary team employing antibiotics, percutaneous drainage of infection, correction of electrolyte and fluid disturbances, initiation of nutritional support, and specialist wound management. Operative intervention is ultimately warranted in most instances, but medical therapy can be appropriately considered for most patients in whom the ECF follows intestinal resection and selected cases in which the ECF is a primary manifestation.

Entero-enteric Fistula in the Setting of Crohn's Disease

Entero-enteric fistulas (EEF) is the second most common type of fistulae observed in CD. Epidemiological studies have reported a 35% risk of a patient with CD developing at least 1 fistula of which one third are EEF.[4] Entero-enteric, entero-colonic, and entero-sigmoid are the most common intra-abdominal fistulae.[202] Symptomology of intra-abdominal fistulae varies considerably and depends on the site of the fistulae. Commonly, fistulae are incidental findings when patients present with symptoms due to stricturing or intra-abdominal inflammatory masses. Fistulae between bowel segments may persist for years before diagnosis and not all diagnosed fistulae need active intervention. Prior to the availability of high resolution imaging approximately one third of intra-abdominal fistulas were diagnosed at surgery or pathological examination, but preoperative diagnosis is more the norm currently. When planning treatment for EEFs, management of associated sepsis, if present, is important prior to any definitive surgery It is also important to plan any potential surgery by correcting underlying malnutrition, obtaining a "road map" of the intestinal anatomy with appropriate imaging, and optimizing medical treatment.

Diagnosis/Symptoms/Presentation

Symptomology of EEFs is nonspecific. Commonly, the investigation of an inflammatory mass is likely to reveal the presence of a fistula. In a minority of cases the symptoms could be attributed to fistulation. The presentation will depend on the site of the fistulation and the associated conditions such as septic foci or malabsorption. The most common manifestation of an EEF is as an inflammatory mass or an abscess. The patient may present with abdominal pain and a tender mass. If an interloop abscess is present, this picture will be complicated with fever and elevated inflammatory markers. The second most common presentation is with intestinal obstruction. The inflammatory mass and the stricturing of the lumen can result in either subacute obstruction or acute intestinal obstruction.

The symptoms attributed to bypassing of the intestinal segment is dependent on the site of the fistula. Short segment ileo-ileal or ileo-colic fistulae may remain asymptomatic as the effects of passing by could be compensated. An ileo-sigmoid fistula will predominantly manifest with diarrhea and possibly signs of malnutrition due to passing by of the absorptive surface.

Another cause for malnutrition in ileo-colic or ileo-sigmoid fistulae is small intestinal bacterial overgrowth (SIBO). Migration of colonic bacteria into the small bowel and growth in the by-passed stagnant section could result in the malabsorption of fat-soluble vitamins and minerals such as calcium. The classical symptoms of SIBO are diarrhea, flatulence, and abdominal pain. The hydrogen breath Test (HBT) which measures the hydrogen concentration in exhaled air after the administration of a glucose load is used as a diagnostic test in SIBO.

A colo-duodenal fistula resulting from colonic disease is also commonly an incidental diagnosis when the patient presents with ileal disease. Although there is feculent content frequently entering the duodenum from the colon, this rarely results in symptoms. Patients who develop duodenal fistulae due to gastroduodenal CD may predominantly have symptoms pertaining to outflow obstruction such as vomiting, regurgitation, and distention. Vomitus containing feculent material may suggest a colo-duodenal fistula. Diarrhea due to bile acids in the colon and SIBO are also not unlikely presentations.

Imaging/Diagnostics

Although imaging techniques have improved over the years, it is not unusual to locate these lesions at surgery.[203] It is not unusual to detect an internal fistula on imaging in an asymptomatic patient during imaging the abdomen for other reasons.[204] The objective of preoperative imaging is to anatomically define the fistula and identify the associated abnormalities such fluid collections and strictures that will be important in surgical decision making. The extent of the expected bowel resection and predicting the possibility of stoma formation also provides adequate time for planning pre and postoperative management of nutrition and helps the process of informed consent. At times when a definite communication between bowel loops is not identified, the imaging can give valuable clues to assess a particular area of the bowel which can be useful at surgery. The classic example would be the situation where there is a suspected ileosigmoid fistula.

MRI has emerged as the choice of imaging in CD. Together with the high detection rates, the noninvasive nature of the examination and the lack of exposure to radiation has made it the investigation of choice. MRE has reported a sensitivity and specificity of 60%-100% and 95%-100%, respectively, in diagnosing enteroenteric fistula preoperatively.[205-207] It requires a gadolinium-based contrast to be administered for the small bowel to be distended and visualized. Although some authorities advocate MR enterochlysis by administering the contrast via a naso-duodenal tube to achieve better jejunal visualization, there is no evidence to suggest that this method gives better results compared to oral administration.[208] An intravenous dose of gadolinium contrast is used to enhance the visualization of the bowel wall and mucosa. A "star-sign" is a classical description of an internal fistula on an MRE comprising of several bowel loops and inflam-

matory sinus tracts converging in to a central point of fistulation. This sign, first described by Hermann and colleagues,[209] however, is not seen in a majority of EEFs.[210] Other features such as perieneteric inflammation and fluid collections have been associated strongly with the presence of fistulae as well as the concomitant presence of hypolabuminaemia.[210]

CTE is still widely used as a diagnostic tool despite the risks associated with radiation and contrast toxicity. CTE provides detailed information on the intra-and extra-luminal changes of CD. A fistulous tract can be visualized as enhancing linear extraluminal tracts connecting bowel loops and could be associated with an abscess. The associated mucosal disease and strictures can be diagnosed with a high sensitivity with CTE due to the mucosal enhancement. Comparison of CTE with MRE has demonstrated noncongruent results. One study demonstrated a higher sensitivity and specificity, with 100% positive predictive value, whereas while others have demonstrated equal sensitivity for both investigations.[205,206]

Small bowel follow-through (SBFT) study was conventionally used in the detection of CD of the small bowel. Its use has declined due to the longer duration and less accuracy compared to CTE and MRE. The flow of contrast material between bowel loops and convergence of the mucosal margins of adjacent bowel loops will be suggestive of an internal fistula. However, due to the limited angles of visualization compared to cross-sectional imaging and increased possibility of artefacts being present the negative predictive value for SBFT is approximately 50%, making it a less reliable test.[205,211]

Upper gastrointestinal endoscopy (UGIE) or colonoscopy will be commonly combined with imaging techniques in managing patients with EEF. Luminal assessment will not provide accurate information regarding fistulae but will be of help to assess the degree of underlying inflammation and stricturing. UGIE may indicate the presence of a colo-duodenal fistula due to flow of feculent material into the lumen. Colonoscopy may help visualize the bile stained small bowel content into the sigmoid colon in an ileo-sigmoid fistula. Double barrel enteroscopy is not routinely performed as a preoperative diagnostic procedure due to its invasive nature.

Medical Management

Current management guidelines recommend early surgical intervention for symptomatic EEF.[212] Evidence supports partial or complete closure of internal fistulae with the use of azathioprine, methotrexate, 6-mercaptopurine, mycophenolate mofetil, cyclosporine A, tacrolimus, or IFX. Data for outcomes from medical management for internal fistulae is lacking compared to data on perianal or enterocutaneous fistulae. Nonethel, IFX, and adalimumab have shown some effect over other biological agents with regards to therapeutic response in fistulating disease.[213,65] Arddizone and colleagues compared azathioprine with methotrexate, and reported comparable results on fistula closure rates[214] while Rosenberg and colleagues in an early study comparing azathioprine with placebo reported no significance.[215] Elemental and polymeric diet have also shown efficacy in closing fistulae. Although neither of the 2 diets have shown superior results over the other, optimizing the patient with either is advised prior to undergoing surgery.[212] Total parenteral nutrition with bowel rest remains a debatable therapeutic modality for ECF, although in enteroenteric fistulae there is no proven benefit. Ileo-sigmoid fistulas have the best response rates to medical therapy; gastro-colic or duodenocolic fistulas generally do not respond to medical therapy and require surgery.[216] Medical management mainly remains an option in patients not fit to undergo surgery or as a trial prior to surgery. Optimizing medical treatment to allow for less intestinal resection has been the strategy in some units, but there has been no clinical evidence to support this hypothesis and optimizing the patent by correcting nutritional and electrolyte abnormalities will be more effective than changing or increasing the dose of medical treatment to facilitate smaller resections.[217]

Postoperative medical therapy has been shown to reduce both clinical and endoscopic recurrence. A recent nationwide cohort study by the French GETAID group has suggested that a strategy of commencing medical therapy early after resection can result in a 0.58 and 0.36 odds ratio of endoscopic and clinical recurrence, respectively. The authors acknowledge that this

finding is in contrast with other studies that suggest that postoperative recurrence is higher in patients with penetrating disease, but they argue that the heterogeneity of these studies could contribute to a bias and the prospective nature of the current study with a definite strategy probably offers better quality evidence.[218]

Operative Intervention

Early operative intervention is recommended for EEF with symptoms. Treatment of intra-abdominal sepsis, prehabilitation, timely surgery to disconnect the fistula, resection of diseased bowel, and release of strictured segments downstream are necessary steps in the surgical management of internal fistulae.

Patients with EEF could present with severe fluid and electrolyte imbalances due to diarrhea. These patients must to be managed at a high dependency setting with adequate fluid and electrolyte replacement. Most EEF could be associated with an extraenteric abscess causing sepsis. It is important to identify these on imaging and address them before surgery is planned. Most collections would be amenable to CT-guided or ultrasound guided aspiration. Antibiotics to settle the intra-abdominal sepsis should be administrated concurrently.

Preoperative optimization of the patient plays a major role in the management of EEF. Some patients might need to be on total parenteral nutrition for a period to reduce the diarrhea and correct nutritional imbalances in order to achieve good postoperative outcomes. The surgical approach can be either open or laparoscopic. The use of laparoscopy has increased over time and this is also so in the case of complex CD such as EEF. The use of laparoscopy may not be associated with increased complications.[219,220] Given the potential for high conversion rates owing to the complex anatomical arrangements, single incision laparoscopic surgery is an option that may allow switching between open and laparoscopic surgery with a smaller scar and could potentially confer additional benefits of laparoscopy such as lower risk of adhesion formation.[221]

Where a fistula is present between the colon and duodenum exists, symptoms such as diarrhea and weight loss may occur. Surgery is usually the treatment for these indications, but if the fistula is asymptomatic then nonsurgical treatment can be considered. Repair of the duodenum can be a primary closure if the defect is small and for a larger defect a jejunal patch or a serosal patch can be performed. The diseased colonic segment should be resected and anastomosed or fashioned as a double-barreled stoma depending on the disease activity, medication use, and nutritional status. It is important to exclude proximal jejunal strictures that could cause failure of the duodenal repair. These patients may require a prolonged period of postoperative parenteral nutrition due to the duodenal repair.

Ileo-ileal EEF can be commonly associated with a phlegmon which requires a longer segment of bowel to be resected. Single port or laparoscopic surgery can be utilized for this procedure as the fistulating segment can be delivered into a wound following minimally invasive mobilization. Resection of the diseased segment with a wider region of the mesentery could potentially reduce the chances of recurrence. The role of an extensive mesenteric excision is in controversial and several approaches of either excluding or resecting diseased mesentery are currently being investigated. [222,223] Where there is extensive stricturing disease, a bowel sparing-approach of resection combined with strictureplasty, where feasible, should be considered.[224]

An ileo-sigmoid fistula requires disconnection of the fistula, resection of the diseased small bowel segment which is usually the terminal or distal ileum, and repair of the sigmoid colon. Although purely anecdotal, the authors suggest that primary repair of the sigmoid colon is possible provided there is no colonic disease. A segmental resection of the sigmoid may be beneficial if there is concomitant disease in the sigmoid colon. In circumstances where there is no detectable fistula after disconnecting the 2 adherent segments, an air leak test with sigmoidoscopy would be prudent to allow detection of a minute defect.

Summary

EEF is associated with significant management challenges which can be compounded when the patient is asymptomatic. A multidisciplinary approach is key to successful management and not only involves the balance of surgical and medical care but also nutritional optimization. Careful planning and understanding the pathological anatomy will help surgical planning. Where there is potential for significant bowel loss, referral to a high volume center should be considered.

Enterovesicular Fistula in the Setting of Crohn's Disease

Diagnosis, Symptoms, and Presentation

EVF is a rare complication of CD, occurring in approximately 2%-8% of all patients.[97] CD is the main cause for EVF, while diverticulitis is the most frequent cause for colovesical fistulas (CVFs), followed by cancer and CD.[225] More recently, a large multicenter retrospective cohort study, including more than 6000 patients from 14 Spanish hospitals, reported a prevalence of 1.6%.[226] Two thirds of the patients had a fistula originating from the terminal ileum, while one fourth of the fistulas occurred between the colon and the bladder. Both types of fistula are explained by the proximity of the respective bowel segment to the bladder. This is also the reason why women are at lower risk: the uterus functions as a barrier to protect the bladder from the source organ. A minority of cases involved the utero-vesicular junction or the urethra, which are much more complex to treat.

An EVF can be simple (a straight connection between the bowel loop and the bladder) or can be part of a more complex fistula, including other bowel loops or the abdominal wall. It can also be complicated by a phlegmon or abscess, which would require appropriate treatment (ie, antibiotics, percutaneous drainage, etc).

Patients with an EVF usually present with recurrent chronic lower urinary tract symptoms, including pneumaturia, fecaluria, mictalgia, urgency, vesical tenesmus, suprapubic pain, and recurrent urinary tract infection. Vesical tenesmus is best described as the feeling of incomplete bladder emptying, which is usually caused by pelvic diaphragmatic spasms.[225] The combination of suprapubic pain, tenesmus, urinary frequency, and mictalgia is also known as the Gouverneur's syndrome.[225] Pneumaturia is a pathognomic symptom for EVF or CVF and is often well described by the patients. In addition to urinary symptoms, patients may also present with GI symptoms, ranging from obstructive symptoms to diarrhea and vague abdominal pain. As mentioned previously, EVF or CVF may be part of more complex fistula or phlegmon/abscess and may be associated with infectious symptoms caused by non-urinary causes.

Imaging/Diagnostics

Cross-sectional imaging is the cornerstone of the diagnostic evaluation in patients with CD. Pooled sensitivity for diagnosis of CD associated fistulas using MRE and CTE have been reported to be 70% and 80%, respectively, with specificity greater than 90%.[227-229] However, sensitivity for the diagnosis of EVFs and CVFs may be higher than 90%, due to indirect signs observed on imaging.[225] Indeed, the fistula as such is often invisible on imaging, however it is usually diagnosed indirectly by the proximity of the bowel loop to the bladder combined with local inflammation and the finding of an intravesical gas bubble. This sign is pathognomic for the diagnosis of an EVF or CVF, unless the patient was catheterized or had any kind of intravesical procedure before imaging. Sometimes, extravasation of intraintestinal contrast dye is seen in the bladder.

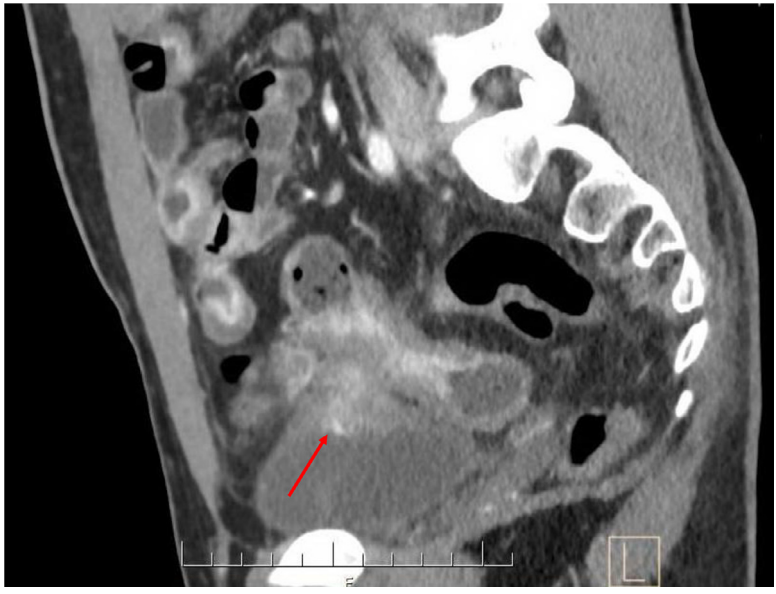

Fig. 7. Sagittal perspective of a CT scan of a young patient with terminal ileal Crohn's disease. No clear enterovesical fistula is visible, however the proximity of the small bowel with the bladder and the local inflammation is very suspicious for a fistula. In addition, oral contrast dye extravasation is visible in the bladder (arrow), confirming the presence of a fistula.

MRE has the major advantage of eliminating the exposure to radiation, even though this exposure has been continuously minimized in modern CT scan protocols.[230] However, an MRE should still be preferred in young patients, who are at risk of multiple radiological investigation along their disease course.

Aside from the formal diagnosis of the fistula, it is important for the surgeons to understand the involvement of the bowel loops, the location of the fistula on the bladder (bladder fundus vs trigone), the presence of any other loops or structures involved and, finally, the presence of any phlegmon or abscess that would require specific management. This thorough assessment will help the surgeon to plan preoperative treatment and surgery and is only possible with a CTE or MRE (Figs 7 and 8).

Ultrasound has been described as a reliable tool for the assessment of CD activity.[231,232] Its accuracy can be increased by the use of contrast-enhancing injections. The injection of hydrogen peroxide in ECFs has been reported.[233] More recently, the injection of contrast in cavities (ie, abscess, bladder, etc) to detect a connection with the bowel loops was reported to significantly increase the accuracy of ultrasound for the detection of fistulas, including EVFs and CVFs.[229,234] The major advantages of ultrasound is the avoidance of radiation and the fact that it is easy to carry and perform bedside procedures.[229] The downside is that it is operator dependent. Moreover, ultrasound images are more difficult for the surgeon to interpret preoperatively.

Plain radiographs or barium studies are not helpful and there is no role for these modalities in the era of highly fidelity cross-sectional imaging techniques.[225] Cystoscopy can be performed but has a pretty low sensitivity in detecting fistulas.[235] It can be helpful to rule out any other bladder related diagnosis (mainly malignancy) or to evaluate the relationship between the fistula and the trigone and the ureteric orifices in cases in which the fistulas are located at the posterior side of the bladder. However, in a recent study, only approximately 10% of patients with a documented fistula underwent a cystoscopy, likely due to the use of modern cross-sectional imaging.[226]

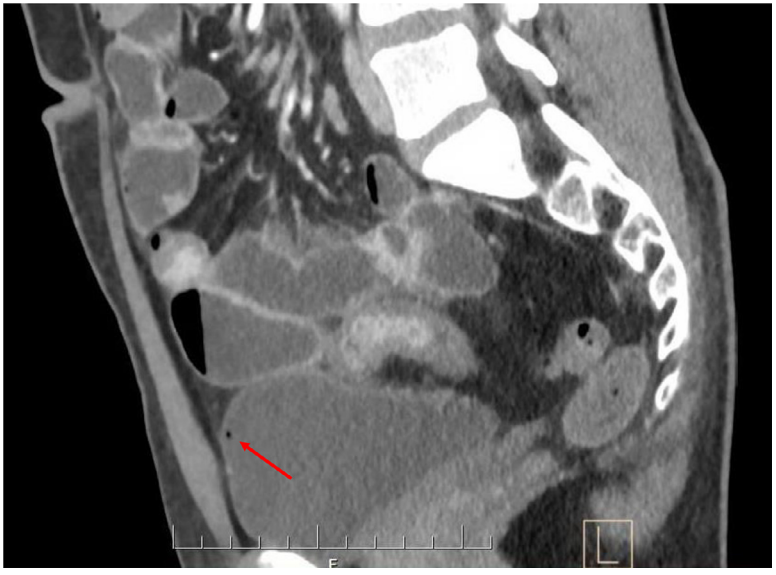

Fig. 8. Another sagittal view of the same patient showing a small intravesical gas bubble (arrow). Notice the diseased bowel loops superior to the bladder, with thickened bowel wall and hyper-enhancing mucosa.

Colonoscopy to identify a CVF as such does not have a high sensitivity. It should therefore not be performed as a diagnostic assessment of the fistula, but remains central in the overall assessment of the extent and severity of colonic and terminal ileal CD.[225]

Medical Management

There is an increased interest in the medical management of EVFs, which used to be an absolute surgical indication. This was driven by the results of several pivotal trials involving TNF-α alpha antagonists, demonstrating the significant impact of those molecules on the closure of intestinal or perianal fistulas.[65,66,236] A recent meta-analysis reviewing all of the available drugs for the treatment of CD demonstrated that the strongest effect estimates to heal CD related fistulas was found for IFX.[237]

None of those trials included patients with EVF, specifically. Therefore, one should be careful when drawing conclusions about the treatment of EVFs on the base of those trials. Medical treatment of EVF has only been reported in very limited case series, with small sample sizes. A recent systematic review including 44 patients with EVF, spread over 19 case series, reported that 57% of those cases showed complete healing with medical therapy, while 36% demonstrated partial response and only 7% showed no healing at all.[97] The studies were of poor quality including nonstandardized treatment regimens, healing assessment, and short-term follow-up. Moreover, healing of the fistula was assessed by imaging in only 1 study.[238] Needless to say, the quality of evidence supporting medical management of CD-related EVF is extremely poor.

Antibiotics play a role in symptomatic control, treating or avoiding urosepsis, and eventually treating an associated intra-abdominal phlegmon or abscess. Long-term healing of EVF with antibiotics has not been reported.

Operative Intervention

Despite increasing interest in medical therapy of EVFs, approximately 80% of all fistulas will ultimately require surgery.[97] The indication for surgery can be 2-sided. First, surgery can be

indicated for the intestinal symptoms. Indeed, when a patient presents with intestinal (partial) obstruction, diarrhea, or abdominal pain, surgery is usually indicated whether there is a fistula or not. On the other hand, in the absence of those symptoms, surgery can still be required to control urinary symptoms that are unresponsive to medical management or after recurrence of the fistula. Intermittent or chronic urinary tract infections with the need for chronic antibiotic treatment is an indication for surgery.

In CD, the fistula usually originates from the terminal ileum and penetrates the bladder fundus. A simple EVF can be operated laparoscopically, acknowledging a slightly increased conversion rate.[239,240] The fistula between the terminal ileum is then divided using blunt and sharp dissection, detaching the small bowel from the bladder. Usually, a locally thickened bladder wall with local inflammation is observed without an obvious opening in the bladder.[241,242] Instillation of the bladder with diluted methylene blue is most often negative and should therefore not be performed routinely.[243] Many authors have proposed not to close the fistula opening in the bladder, but rather drain the bladder using a Foley catheter for approximately a week.[242,244,245] It has indeed been demonstrated that re-epithelialization of the bladder occurs within a week.[246] In the event that a larger hole is found in the bladder, surgical repair is indicated which is performed in 1 or 2 layers of running absorbable sutures. Excision of the inflamed borders of the fistula opening can be necessary in order to obtain healthier tissue for suture repair. This can be performed by experienced colorectal surgeons and urologists usually do not need to be involved. Omental flapping to cover the bladder opening with a well vascularized tissue flap has been described but is probably not necessary in the context of EVFs for CD, given the extremely high rates of healing with or without suture repair alone.[241]

In more complex cases, in which the fistula is situated at the posterior side of the bladder and involving the trigone, operative repair is much more challenging. Ureteric re-implantation and more complex bladder surgery is often required and one should always involve the participation of a urologist experienced in complex bladder surgery.

The intestinal resection is performed as usual, resecting either the ileocolic segment including the resection or repair of any other structure involved in the disease process. If the colon is the source organ, this segment will be resected. The presence of a fistula to the bladder alone is not a sufficient reason for a stoma, but the decision to perform fecal diversion should be based on the presence of sepsis or patient's general (nutritional) condition.

Laparoscopic surgery is usually possible with simple fistulas. However, fistulas invading the posterior wall of the bladder, close to the trigone, should be operated conventionally, using a midline laparotomy. In addition, complex fistulas invading the retroperitoneum should also be performed by laparotomy to ensure safe dissection of the bowel package off the retroperitoneal plane.

Postoperative management of EVFs requires a prolonged catheterization of the bladder. This avoids increased intravesical pressure to allow the fistula to heal. There is no consensus in the literature on the length of time the bladder should be catheterized and whether a cystogram is needed before catheter removal. Most small case series report a catheterization period between 7 and 10 days, with a cystogram before removal.[241,243,245,247] However, cystograms after prolonged bladder drainage are rarely positive and positive tests usually occur after complex bladder repair.[243] Therefore, the authors suggest to reserve cystograms for complex bladder repairs. A cystogram after a simple fistula which did not need any repair, probably does not require imaging.[243] Prolonged bladder catheterization should not extend patient admission, as they can usually be discharged with a catheter which can be removed in an outpatient setting. The authors suggest that 7 days of bladder drainage is sufficient for all but the most complex bladder repairs. More data are required to make strong recommendations on both the interval for bladder catheterization and the need of cystograms.

Concluding Remarks

CD is a chronic disease characterized by transmural inflammation resulting in fistula formation. This can occur anywhere along the GI tract and perianally. The symptoms can result in debilitating pain, drainage, and incontinence depending on the location. Medical therapy with biologics is unfortunately not particularly effective, and most patients require some sort of surgical intervention to at least control the associated sepsis. The morbidity of this phenotype is underscored by the multiple medications and surgical interventions it takes to provide symptom relief, and in some cases, eradication of the fistula. Novel therapies such as MSCs may provide improved treatment options, but we are still a long way from this being widely used across multiple phenotypes. Until then, multidisciplinary management with radiologists, gastroenterologists, and surgeons provides optimal treatment pathways for patients with fistulizing CD.

References

1. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD).. *Gut*. 1996;39:690–697.
2. Burisch J, Jess T, Martinato M, Lakatos PL, EpiCom E. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis*. 2013;7:322–337.
3. Yu AP, Cabanilla LA, Wu EQ, Mulani PM, Chao J. The costs of Crohn's disease in the United States and other Western countries: a systematic review. *Curr Med Res Opin*. 2008;24:319–328.
4. Schwartz DA, Loftus Jr EV, Tremaine WJ, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology*. 2002;122:875–880.
5. Bissell AD. Localized chronic ulcerative ileitis. *Ann Surg*. 1934;99:957–966.
6. Crohn BB, Ginzberg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. *JAMA*. 1932;99:1323–1329.
7. Morson BC, Lockhart-Mummery HE. Anal lesions in Crohn's disease. *Lancet*. 1959;2:1122–1123.
8. Gray BK, Lockhartmummery HE, Morson BC. Crohn's disease of the anal region. *Gut*. 1965;6:515–524.
9. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142:46–54.
10. Kanaan Z, Ahmad S, Bilchuk N, Vahrenhold C, Pan J, Galandiuk S. Perianal Crohn's disease: predictive factors and genotype-phenotype correlations. *Dig Surg*. 2012;29:107–114.
11. Chan SS, Luben R, Olsen A, et al. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). *Am J Gastroenterol*. 2013;108:575–582.
12. Binder V. Epidemiology of IBD during the twentieth century: an integrated view. *Best Pract Res Clin Gastroenterol*. 2004;18:463–479.
13. American Gastroenterological Association Clinical Practice C. American Gastroenterological Association medical position statement: perianal Crohn's disease. *Gastroenterology*. 2003;125:1503–1507.
14. Bataille F, Klebl F, Rummele P, et al. Morphological characterisation of Crohn's disease fistulae. *Gut*. 2004;53:1314–1321.
15. Solomon MJ. Fistulae and abscesses in symptomatic perianal Crohn's disease. *Int J Colorectal Dis*. 1996;11:222–226.
16. Fielding JF. Perianal lesions in Crohn's disease. *J R Coll Surg Edinb*. 1972;17:32–37.
17. Lockhart-Mummery HE. Symposium. Crohn's disease: anal lesions. *Dis Colon Rectum*. 1975;18:200–202.
18. McClane SJ, Rombeau JL. Anorectal Crohn's disease. *Surg Clin North Am*. 2001;81:169–183.
19. Rankin GB, Watts HD, Melnyk CS, Kelley Jr ML. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. *Gastroenterology*. 1979;77:914–920.
20. Tarrant KM, Barclay ML, Frampton CM, Gearry RB. Perianal disease predicts changes in Crohn's disease phenotype-results of a population-based study of inflammatory bowel disease phenotype. *Am J Gastroenterol*. 2008;103:3082–3093.
21. Eglinton TW, Roberts R, Pearson J, et al. Clinical and genetic risk factors for perianal Crohn's disease in a population-based cohort. *Am J Gastroenterol*. 2012;107:589–596.
22. Eglinton TW, Barclay ML, Gearry RB, Frizelle FA. The spectrum of perianal Crohn's disease in a population-based cohort. *Dis Colon Rectum*. 2012;55:773–777.
23. Hellers G, Bergstrand O, Ewerth S, Holmstrom B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. *Gut*. 1980;21:525–527.
24. Lapidus A. Crohn's disease in Stockholm County during 1990-2001: an epidemiological update. *World J Gastroenterol*. 2006;12:75–81.
25. Tang LY, Rawsthorne P, Bernstein CN. Are perineal and luminal fistulas associated in Crohn's disease? A population-based study. *Clin Gastroenterol Hepatol*. 2006;4:1130–1134.
26. Gecse KB, Sebastian S, Hertogh G, et al. Results of the Fifth Scientific Workshop of the ECCO [II]: clinical aspects of perianal fistulising Crohn's disease, the unmet needs. *J Crohns Colitis*. 2016;10:758–765.
27. Cross RK, Jung C, Wasan S, Joshi G, Sawyer R, Roghmann MC. Racial differences in disease phenotypes in patients with Crohn's disease. *Inflamm Bowel Dis*. 2006;12:192–198.

28. Nguyen GC, Torres EA, Regueiro M, et al. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort. *Am J Gastroenterol*. 2006;101:1012–1023.
29. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis*. 2002;8:244–250.
30. Bergstrand O, Ewerth S, Hellers G, Holmstrom B, Ullman J, Wallberg P. Outcome following treatment of anal fistulae in Crohn's disease. *Acta Chir Scand Suppl*. 1980;500:43–44.
31. Radcliffe AG, Ritchie JK, Hawley PR, Lennard-Jones JE, Northover JM. Anovaginal and rectovaginal fistulas in Crohn's disease. *Dis Colon Rectum*. 1988;31:94–99.
32. Saclarides TJ. Rectovaginal fistula. *Surg Clin North Am*. 2002;82:1261–1272.
33. Schaffzin DM, Stahl TJ, Smith LE. Perianal mucinous adenocarcinoma: unusual case presentations and review of the literature. *Am Surg*. 2003;69:166–169.
34. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. *Br J Surg*. 1976;63:1–12.
35. Morris J, Spencer JA, Ambrose NS. MR imaging classification of perianal fistulas and its implications for patient management. *Radiographics*. 2000;20:623–635.
36. Hughes LE. Surgical pathology and management of anorectal Crohn's disease. *J R Soc Med*. 1978;71:644–651.
37. Bemelman WA, Warusavitarne J, Sampietro GM, et al. ECCO-ESCP consensus on surgery for Crohn's disease. *J Crohns Colitis*. 2018;12:1–16.
38. Gasche C, Scholmerich J, Brynskov J, et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis*. 2000;6:8–15.
39. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol*. 2005;19(Suppl A):5A–36A.
40. Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB. American Gastroenterological Association Clinical Practice C. AGA technical review on perianal Crohn's disease. *Gastroenterology*. 2003;125:1508–1530.
41. Kotze PG, Shen B, Lightner A, et al. Modern management of perianal fistulas in Crohn's disease: future directions. *Gut*. 2018;67:1181–1194.
42. Lillie FR. *The development of the chick: an introduction to embryology*. New York (NY): Henry Holt and Co; 1908.
43. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest*. 2009;119:1420–1428.
44. Kirkegaard T, Hansen A, Bruun E, Brynskov J. Expression and localisation of matrix metalloproteinases and their natural inhibitors in fistulae of patients with Crohn's disease. *Gut*. 2004;53:701–709.
45. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361:2066–2078.
46. Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature*. 2001;411:603–606.
47. Van Limbergen J, Russell RK, Nimmo ER, et al. Genetics of the innate immune response in inflammatory bowel disease. *Inflamm Bowel Dis*. 2007;13:338–355.
48. Csongei V, Jaromi L, Safrany E, et al. Interaction of the major inflammatory bowel disease susceptibility alleles in Crohn's disease patients. *World J Gastroenterol*. 2010;16:176–183.
49. Armuzzi A, Ahmad T, Ling KL, et al. Genotype-phenotype analysis of the Crohn's disease susceptibility haplotype on chromosome 5q31. *Gut*. 2003;52:1133–1139.
50. Chanal J, Duong TA, Valeyrie-Allanore L, et al. Necrotizing fasciitis of the thigh revealing a Crohn's disease. *J Eur Acad Dermatol Venereol*. 2015;29:1648–1649.
51. Wood SC. Clinical manifestations and therapeutic management of vulvar cellulitis and abscess: methicillin-resistant staphylococcus aureus, necrotizing fasciitis, bartholin abscess, Crohn disease of the vulva, hidradenitis suppurativa. *Clin Obstet Gynecol*. 2015;58:503–511.
52. Coremans G, Dockx S, Wyndaele J, Hendrickx A. Do anal fistulas in Crohn's disease behave differently and defy Goodsall's rule more frequently than fistulas that are cryptoglandular in origin? *Am J Gastroenterol*. 2003;98:2732–2735.
53. Teoule P, Seyfried S, Joos A, Bussen D, Herold A. Management of retrorectal supralevator abscess-results of a large cohort. *Int J Colorectal Dis*. 2018;33:1589–1594.
54. Ilias A, Lovasz BD, Gonczi L, et al. Optimizing patient management in Crohn's disease in a tertiary referral center: the impact of Fast-Track MRI on patient management and outcomes. *J Gastrointestin Liver Dis*. 2018;27:391–397.
55. Ong EM, Ghazi LJ, Schwartz DA, Mortele KJ. Crohn's, Colitis Foundation of America I. Guidelines for imaging of Crohn's perianal fistulizing disease. *Inflamm Bowel Dis*. 2015;21:731–736.
56. Vernuccio F, Picone D, Midiri F, Salerno S, Lagalla R, Lo Re G. MR imaging of perianal Crohn disease: the role of contrast-enhanced sequences. *Radiology*. 2017;284:921–922.
57. Sheedy SP, Bruining DH, Dozois EJ, Faubion WA, Fletcher JG. MR imaging of perianal Crohn disease. *Radiology*. 2017;282:628–645.
58. Bruining DH, Zimmermann EM, Loftus Jr EV, et al. Consensus recommendations for evaluation, interpretation, and utilization of computed tomography and magnetic resonance enterography in patients with small bowel Crohn's disease. *Radiology*. 2018;286:776–799.
59. de la Portilla F, Duran V, Maestre MV, et al. Effectiveness of a three-dimensional anorectal ultrasound in perianal Crohn's disease: incompatibility with clinical and surgical examinations. *Int J Colorectal Dis*. 2015;30:529–534.
60. Hatch Q, Champagne BJ, Maykel JA, et al. Crohn's disease and pregnancy: the impact of perianal disease on delivery methods and complications. *Dis Colon Rectum*. 2014;57:174–178.
61. Beaugerie L, Carrat F, Nahon S, et al. High risk of anal and rectal cancer in patients with anal and/or perianal Crohn's disease. *Clin Gastroenterol Hepatol*. 2018;16:892–899 e2.
62. Thia KT, Mahadevan U, Feagan BG, et al. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis*. 2009;15:17–24.

63. Dewint P, Hansen BE, Verhey E, et al. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). *Gut*. 2014;63:292–299.
64. Pearson DC, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease: a meta-analysis. *Ann Intern Med*. 1995;123:132–142.
65. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med*. 1999;340:1398–1405.
66. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350:876–885.
67. Colombel JF, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut*. 2009;58:940–948.
68. Fu YM, Chen M, Liao AJ. A meta-analysis of adalimumab for fistula in Crohn's disease. *Gastroenterol Res Pract*. 2017;2017.
69. Schreiber S, Lawrance IC, Thomsen OO, Hanauer SB, Bloomfield R, Sandborn WJ. Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease: subgroup results from a placebo-controlled study. *Aliment Pharmacol Ther*. 2011;33:185–193.
70. Strik AS, Lowenberg M, Buskens CJ, et al. Higher anti-TNF serum levels are associated with perianal fistula closure in Crohn's disease patients. *Scand J Gastroenterol*. 2019;54:453–458.
71. Kotze PG, Albuquerque IC, da Luz Moreira A, Tonini WB, Olandoski M, Coy CS. Perianal complete remission with combined therapy (seton placement and anti-TNF agents) in Crohn's disease: a Brazilian multicenter observational study. *Arq Gastroenterol*. 2014;51:284–289.
72. Regueiro M, Mardini H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. *Inflamm Bowel Dis*. 2003;9:98–103.
73. Rozalen V, Pares D, Sanchez E, et al. Advancement flap technique for anal fistula in patients with Crohn's disease: a systematic review of the literature. *Cir Esp*. 2017;95:558–565.
74. Kaminski JP, Zaghiyan K, Fleshner P. Increasing experience of ligation of the intersphincteric fistula tract for patients with Crohn's disease: what have we learned? *Colorectal Dis*. 2017;19:750–755.
75. Grimaud JC, Munoz-Bongrand N, Siproudhis L, et al. Fibrin glue is effective healing perianal fistulas in patients with Crohn's disease. *Gastroenterology*. 2010;138:2275–2281.
76. Senejoux A, Siproudhis L, Abramowitz L, et al. Fistula plug in fistulising ano-perineal Crohn's disease: a randomised controlled trial. *J Crohns Colitis*. 2016;10:141–148.
77. Adegbola SO, Sahnan K, Tozer PJ, et al. Symptom amelioration in Crohn's perianal fistulas using video assisted anal fistula treatment (VAAFT). *J Crohns Colitis*. 2018.
78. Wilhelm A, Fiebig A, Krawczak M. Five years of experience with the FiLaC laser for fistula-in-ano management: long-term follow-up from a single institution. *Tech Coloproctol*. 2017;21:269–276.
79. Singh S, Ding NS, Mathis KL, et al. Systematic review with meta-analysis: faecal diversion for management of perianal Crohn's disease. *Aliment Pharmacol Ther*. 2015;42:783–792.
80. Garcia-Olmo D, Garcia-Arranz M, Herreros D, Pascual I, Peiro C, Rodriguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. *Dis Colon Rectum*. 2005;48:1416–1423.
81. Serena C, Keiran N, Madeira A, et al. Crohn's disease disturbs the immune properties of human adipose-derived stem cells related to inflammasome activation. *Stem Cell Reports*. 2017;9:1109–1123.
82. Lightner AL, Wang Z, Zubair AC, Dozois EJ. A systematic review and meta-analysis of mesenchymal stem cell injections for the treatment of perianal Crohn's disease: progress made and future directions. *Dis Colon Rectum*. 2018;61:629–640.
83. Panes J, Garcia-Olmo D, Van Assche G, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet*. 2016;388:1281–1290.
84. Panes J, Garcia-Olmo D, Van Assche G, et al. Long-term efficacy and safety of stem cell therapy (Cx601) for complex perianal fistulas in patients with Crohn's disease. *Gastroenterology*. 2018;154:1334–1342.
85. Scharl M, Rogler G. Pathophysiology of fistula formation in Crohn's disease. *World J Gastrointest Pathophysiol*. 2014;5:205–212.
86. Bagby RJ, Clements Jr JL, Patrick JW, Rogers JV, Weens HS. Genitourinary complications of granulomatous bowel disease. *Am J Roentgenol Radium Ther Nucl Med*. 1973;117:297–306.
87. Narang R, Hull T, Perrins S, Garcia JS, Wexner SD. Should immunomodulation therapy alter the surgical management in patients with rectovaginal fistula and Crohn's disease? *Dis Colon Rectum*. 2016;59:670–676.
88. Schwartz DA, Maltz BE. Treatment of fistulizing inflammatory bowel disease. *Gastroenterol Clin North Am*. 2009;38:595–610.
89. Hayashi C, Takada S, Kasuga A, et al. Sigmoid-vaginal fistula during bevacizumab treatment diagnosed by fistulography. *J Clin Pharm Ther*. 2016;41:725–726.
90. Shobeiri SA, Quiroz L, Nihira M. Rectovaginal fistulography: a technique for the identification of recurrent elusive fistulas. *Int Urogynecol J Pelvic Floor Dysfunct*. 2009;20:571–573.
91. Meinero P, Mori L. Video-assisted anal fistula treatment (VAAFT): a novel sphincter-saving procedure for treating complex anal fistulas. *Tech Coloproctol*. 2011;15:417–422.
92. Schwandner O. Video-assisted anal fistula treatment (VAAFT) combined with advancement flap repair in Crohn's disease. *Tech Coloproctol*. 2013;17:221–225.
93. Present DH. Crohn's fistula: current concepts in management. *Gastroenterology*. 2003;124:1629–1635.
94. Korelitz BI, Present DH. Favorable effect of 6-mercaptopurine on fistulae of Crohn's disease. *Dig Dis Sci*. 1985;30:58–64.

95. Mahadevan U, Marion JF, Present DH. Fistula response to methotrexate in Crohn's disease: a case series. *Aliment Pharmacol Ther*. 2003;18:1003–1008.
96. Gonzalez-Lama Y, Abreu L, Vera MI, et al. Long-term oral tacrolimus therapy in refractory to infliximab fistulizing Crohn's disease: a pilot study. *Inflamm Bowel Dis*. 2005;11:8–15.
97. Kaimakliotis P, Simillis C, Harbord M, Kontovounisios C, Rasheed S, Tekkis PP. A systematic review assessing medical treatment for rectovaginal and enterovesical fistulae in Crohn's disease. *J Clin Gastroenterol*. 2016;50:714–721.
98. Egan LJ, Sandborn WJ, Tremaine WJ. Clinical outcome following treatment of refractory inflammatory and fistulizing Crohn's disease with intravenous cyclosporine. *Am J Gastroenterol*. 1998;93:442–448.
99. Ardizzone S, Maconi G, Colombo E, Manzionna G, Bollani S, Bianchi Porro G. Perianal fistulae following infliximab treatment: clinical and endosonographic outcome. *Inflamm Bowel Dis*. 2004;10:91–96.
100. de Ridder L, Escher JC, Bouquet J, et al. Infliximab therapy in 30 patients with refractory pediatric crohn disease with and without fistulas in The Netherlands. *J Pediatr Gastroenterol Nutr*. 2004;39:46–52.
101. Miheller P, Lakatos PL, Horvath G, et al. Efficacy and safety of infliximab induction therapy in Crohn's Disease in Central Europe: a Hungarian nationwide observational study. *BMC Gastroenterol*. 2009;9:66.
102. Ng SC, Plamondon S, Gupta A, et al. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas. *Am J Gastroenterol*. 2009;104:2973–2986.
103. Parsi MA, Lashner BA, Achkar JP, Connor JT, Brzezinski A. Type of fistula determines response to infliximab in patients with fistulous Crohn's disease. *Am J Gastroenterol*. 2004;99:445–449.
104. Poritz LS, Rowe WA, Koltun WA. Remicade does not abolish the need for surgery in fistulizing Crohn's disease. *Dis Colon Rectum*. 2002;45:771–775.
105. Sands BE, Blank MA, Patel K, van Deventer SJ, Study AI. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. *Clin Gastroenterol Hepatol*. 2004;2:912–920.
106. Swoger JM, Loftus Jr EV, Tremaine WJ, et al. Adalimumab for Crohn's disease in clinical practice at Mayo Clinic: the first 118 patients. *Inflamm Bowel Dis*. 2010;16:1912–1921.
107. van Bodegraven AA, Sloots CE, Felt-Bersma RJ, Meuwissen SG. Endosonographic evidence of persistence of Crohn's disease-associated fistulas after infliximab treatment, irrespective of clinical response. *Dis Colon Rectum*. 2002;45:39–45.
108. Gaertner WB, Witt J, Madoff RD, Mellgren A, Finne CO, Spencer MP. Ileal pouch fistulas after restorative proctocolectomy: management and outcomes. *Tech Coloproctol*. 2014;18:1061–1066.
109. Ruffolo C, Penninckx F, Van Assche G, et al. Outcome of surgery for rectovaginal fistula due to Crohn's disease. *Br J Surg*. 2009;96:1190–1195.
110. El-Gazzaz G, Hull T, Mignanelli E, Hammel J, Gurland B, Zutshi M. Analysis of function and predictors of failure in women undergoing repair of Crohn's related rectovaginal fistula. *J Gastrointest Surg*. 2010;14:824–829.
111. Sonoda T, Hull T, Piedmonte MR, Fazio VW. Outcomes of primary repair of anorectal and rectovaginal fistulas using the endorectal advancement flap. *Dis Colon Rectum*. 2002;45:1622–1628.
112. Abelson JS, Michelassi F, Mao J, Sedrakyan A, Yeo H. Higher surgical morbidity for ulcerative colitis patients in the era of biologics. *Ann Surg*. 2018;268:311–317.
113. Furst A, Schmidbauer C, Swol-Ben J, Iesalnieks I, Schwandner O, Agha A. Gracilis transposition for repair of recurrent anovaginal and rectovaginal fistulas in Crohn's disease. *Int J Colorectal Dis*. 2008;23:349–353.
114. Makowiec F, Jehle EC, Becker HD, Starlinger M. Clinical course after transanal advancement flap repair of perianal fistula in patients with Crohn's disease. *Br J Surg*. 1995;82:603–606.
115. Schwandner O, Fuerst A. Preliminary results on efficacy in closure of transsphincteric and rectovaginal fistulas associated with Crohn's disease using new biomaterials. *Surg Innov*. 2009;16:162–168.
116. O'Leary DP, Milroy CE, Durdey P. Definitive repair of anovaginal fistula in Crohn's disease. *Ann R Coll Surg Engl*. 1998;80:250–252.
117. Gaertner WB, Madoff RD, Spencer MP, Mellgren A, Goldberg SM, Lowry AC. Results of combined medical and surgical treatment of recto-vaginal fistula in Crohn's disease. *Colorectal Dis*. 2011;13:678–683.
118. Penninckx F, Moneghini D, D'Hoore A, Wyndaele J, Coremans G, Rutgeerts P. Success and failure after repair of rectovaginal fistula in Crohn's disease: analysis of prognostic factors. *Colorectal Dis*. 2001;3:406–411.
119. Hull TL, Fazio VW. Surgical approaches to low anovaginal fistula in Crohn's disease. *Am J Surg*. 1997;173:95–98.
120. Jones IT, Fazio VW, Jagelman DG. The use of transanal rectal advancement flaps in the management of fistulas involving the anorectum. *Dis Colon Rectum*. 1987;30:919–923.
121. Joo JS, Weiss EG, Nogueras JJ, Wexner SD. Endorectal advancement flap in perianal Crohn's disease. *Am Surg*. 1998;64:147–150.
122. Ozuner G, Hull TL, Cartmill J, Fazio VW. Long-term analysis of the use of transanal rectal advancement flaps for complicated anorectal/vaginal fistulas. *Dis Colon Rectum*. 1996;39:10–14.
123. Athanasiadis S, Yazigi R, Kohler A, Helmes C. Recovery rates and functional results after repair for rectovaginal fistula in Crohn's disease: a comparison of different techniques. *Int J Colorectal Dis*. 2007;22:1051–1060.
124. Hesterberg R, Schmidt WU, Muller F, Roher HD. Treatment of anovaginal fistulas with an anocutaneous flap in patients with Crohn's disease. *Int J Colorectal Dis*. 1993;8:51–54.
125. Morrison JG, Gathright Jr JB, Ray JE, Ferrari BT, Hicks TC, Timmcke AE. Results of operation for rectovaginal fistula in Crohn's disease. *Dis Colon Rectum*. 1989;32:497–499.
126. Nosti PA, Stahl TJ, Sokol AI. Surgical repair of rectovaginal fistulas in patients with Crohn's disease. *Eur J Obstet Gynecol Reprod Biol*. 2013;171:166–170.
127. Pinto RA, Peterson TV, Shawki S, Davila GW, Wexner SD. Are there predictors of outcome following rectovaginal fistula repair? *Dis Colon Rectum*. 2010;53:1240–1247.
128. Sher ME, Bauer JJ, Gelernt I. Surgical repair of rectovaginal fistulas in patients with Crohn's disease: transvaginal approach. *Dis Colon Rectum*. 1991;34:641–648.
129. Windsor L, Khan R, Williams N. Rectovaginal fistulae in Crohn's disease: a management paradox. *Colorectal Dis*. 2000;2:154–158.

130. Rojanasakul A, Pattanaarun J, Sahakitrungruang C, Tantiphlachiva K. Total anal sphincter saving technique for fistula-in-ano; the ligation of intersphincteric fistula tract. *J Med Assoc Thai*. 2007;90:581–586.
131. Bleier JI, Moloo H, Goldberg SM. Ligation of the intersphincteric fistula tract: an effective new technique for complex fistulas. *Dis Colon Rectum*. 2010;53:43–46.
132. Lehmann JP, Graf W. Efficacy of LIFT for recurrent anal fistula. *Colorectal Dis*. 2013;15:592–595.
133. Sileri P, Franceschilli L, Angelucci GP, et al. Ligation of the intersphincteric fistula tract (LIFT) to treat anal fistula: early results from a prospective observational study. *Tech Coloproctol*. 2011;15:413–416.
134. Ellis CN. Outcomes after repair of rectovaginal fistulas using bioprosthetics. *Dis Colon Rectum*. 2008;51:1084–1088.
135. Gingold DS, Murrell ZA, Fleshner PR. A prospective evaluation of the ligation of the intersphincteric tract procedure for complex anal fistula in patients with Crohn's disease. *Ann Surg*. 2014;260:1057–1061.
136. Milito G, Lisi G, Venditti D, Campanelli M, Aronadio E, Grande M. Surgical treatment of rectovaginal fistula in Crohn's disease: a tertiary center experience. *Surg Technol Int*. 2017;30:113–116.
137. Songne K, Scotte M, Lubrano J, et al. Treatment of anovaginal or rectovaginal fistulas with modified Martius graft. *Colorectal Dis*. 2007;9:653–656.
138. Wexner SD, Ruiz DE, Genua J, Nogueras JJ, Weiss EG, Zmora O. Gracilis muscle interposition for the treatment of rectourethral, rectovaginal, and pouch-vaginal fistulas: results in 53 patients. *Ann Surg*. 2008;248:39–43.
139. Bandy LC, Addison A, Parker RT. Surgical management of rectovaginal fistulas in Crohn's disease. *Am J Obstet Gynecol*. 1983;147:359–363.
140. Mege D, Frasson M, Maggiori L, Panis Y. Is biological mesh interposition a valid option for complex or recurrent rectovaginal fistula? *Colorectal Dis*. 2016;18:O61–O65.
141. El-Gazzaz G, Zutshi M, Hull T. A retrospective review of chronic anal fistulae treated by anal fistulae plug. *Colorectal Dis*. 2010;12:442–447.
142. DelaRosa O, Dalemans W, Lombardo E. Mesenchymal stem cells as therapeutic agents of inflammatory and autoimmune diseases. *Curr Opin Biotechnol*. 2012;23:978–983.
143. Garcia-Olmo D, Herreros D, Pascual I, et al. Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. *Dis Colon Rectum*. 2009;52:79–86.
144. Dozois EJ, Lightner AL, Mathis KL, et al. Early results of a phase I trial using an adipose-derived mesenchymal stem cell-coated fistula plug for the treatment of transsphincteric cryptoglandular fistulas. *Dis Colon Rectum*. 2019;62:615–622.
145. Lightner AL, Dozois EJ, Dietz AB, et al. Matrix-delivered autologous mesenchymal stem cell therapy for refractory rectovaginal Crohn's fistulas. *Inflamm Bowel Dis*. 2020;26(5):670–677.
146. Heyen F, Winslet MC, Andrews H, Alexander-Williams J, Keighley MR. Vaginal fistulas in Crohn's disease. *Dis Colon Rectum*. 1989;32:379–383.
147. Kodner IJ, Mazor A, Shemesh EI, Fry RD, Fleshman JW, Birnbaum EH. Endorectal advancement flap repair of rectovaginal and other complicated anorectal fistulas. *Surgery*. 1993;114:682–689.
148. MacRae HM, McLeod RS, Cohen Z, Stern H, Reznick R. Treatment of rectovaginal fistulas that has failed previous repair attempts. *Dis Colon Rectum*. 1995;38:921–925.
149. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. *Br Med J*. 1978;2:85–88.
150. Heikens JT, de Vries J, van Laarhoven CJ. Quality of life, health-related quality of life and health status in patients having restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis: a systematic review. *Colorectal Dis*. 2012;14:536–544.
151. Lightner AL, Mathis KL, Dozois EJ, et al. Results at up to 30 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Inflamm Bowel Dis*. 2017;23:781–790.
152. Worley GHT, Fearnhead NS, Brown SR, et al. Review of current practice and outcomes following ileoanal pouch surgery: lessons learned from the Ileoanal Pouch Registry and the 2017 Ileoanal Pouch Report. *Colorectal Dis*. 2018;20:913–922.
153. Lolohea S, Lynch AC, Robertson GB, Frizelle FA. Ileal pouch-anal anastomosis-vaginal fistula: a review. *Dis Colon Rectum*. 2005;48:1802–1810.
154. Peirce C, Remzi FH. Operative strategy, risk factors for leak, and the use of a defunctioning ileostomy with ileal pouch-anal anastomosis: let's not divert from diversion and the traditional 3-stage approach for inflammatory bowel disease. *J Crohns Colitis*. 2016;10:755–757.
155. Weston-Petrides GK, Lovegrove RE, Tilney HS, et al. Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy. *Arch Surg*. 2008;143:406–412.
156. Grobler SP, Hosie KB, Keighley MR. Randomized trial of loop ileostomy in restorative proctocolectomy. *Br J Surg*. 1992;79:903–906.
157. Mark-Christensen A, Kjaer MD, Ganesalingam S, et al. Increasing incidence of pelvic sepsis following ileal pouch-anal anastomosis for ulcerative colitis in Denmark: a nationwide cohort study. *Dis Colon Rectum*. 2019;62:965–971.
158. Shen B, Remzi FH, Lavery IC, Lashner BA, Fazio VW. A proposed classification of ileal pouch disorders and associated complications after restorative proctocolectomy. *Clin Gastroenterol Hepatol*. 2008;6:145–158.
159. Prudhomme M, Dehni N, Dozois RR, Tiret E, Parc R. Causes and outcomes of pouch excision after restorative proctocolectomy. *Br J Surg*. 2006;93:82–86.
160. Nisar PJ, Kiran RP, Shen B, Remzi FH, Fazio VW. Factors associated with ileoanal pouch failure in patients developing early or late pouch-related fistula. *Dis Colon Rectum*. 2011;54:446–453.
161. Reza L, Lung PFC, Lightner AL, Hart A, Clark SK, Tozer P. Perianal fistula and the ileoanal pouch: different aetiologies require distinct evaluation. *Colorectal Dis*. 2019.
162. Keighley MR, Grobler SP. Fistula complicating restorative proctocolectomy. *Br J Surg*. 1993;80:1065–1067.
163. Kiran RP, da Luz Moreira A, Remzi FH, et al. Factors associated with septic complications after restorative proctocolectomy. *Ann Surg*. 2010;251:436–440.

164. Sahnan K, Askari A, Adegbola SO, et al. Persistent fistula after anorectal abscess drainage: local experience of 11 years. *Dis Colon Rectum*. 2019;62:327–332.
165. Shen B. *Pouchitis and ileal pouch disorders*. Medical therapy for Crohn's disease of the pouch. Cambridge (MA): Elsevier; 2019.
166. Shen B, Fazio VW, Remzi FH, et al. Combined ciprofloxacin and tinidazole therapy in the treatment of chronic refractory pouchitis. *Dis Colon Rectum*. 2007;50:498–508.
167. Chopra A, Pardi DS, Loftus Jr EV, et al. Budesonide in the treatment of inflammatory bowel disease: the first year of experience in clinical practice. *Inflamm Bowel Dis*. 2006;12:29–32.
168. Sandborn WJ, Lofberg R, Feagan BG, Hanauer SB, Campieri M, Greenberg GR. Budesonide for maintenance of remission in patients with Crohn's disease in medically induced remission: a predetermined pooled analysis of four randomized, double-blind, placebo-controlled trials. *Am J Gastroenterol*. 2005;100:1780–1787.
169. Berrebi W, Chaussade S, Bruhl AL, et al. Treatment of Crohn's disease recurrence after ileoanal anastomosis by azathioprine. *Dig Dis Sci*. 1993;38:1558–1560.
170. Haveran LA, Sehgal R, Poritz LS, McKenna KJ, Stewart DB, Koltun WA. Infliximab and/or azathioprine in the treatment of Crohn's disease-like complications after IPAA. *Dis Colon Rectum*. 2011;54:15–20.
171. Colombel JF, Ricart E, Loftus Jr EV, et al. Management of Crohn's disease of the ileoanal pouch with infliximab. *Am J Gastroenterol*. 2003;98:2239–2244.
172. Ferrante M, D'Haens G, Dewit O, et al. Efficacy of infliximab in refractory pouchitis and Crohn's disease-related complications of the pouch: a Belgian case series. *Inflamm Bowel Dis*. 2010;16:243–249.
173. Mallick IH, Hull TL, Remzi FH, Kiran RP. Management and outcome of pouch-vaginal fistulas after IPAA surgery. *Dis Colon Rectum*. 2014;57:490–496.
174. Li Y, Lopez R, Queener E, Shen B. Adalimumab therapy in Crohn's disease of the ileal pouch. *Inflamm Bowel Dis*. 2012;18:2232–2239.
175. Gu J, Stocchi L, Kiran RP, Shen B, Remzi FH. Do clinical characteristics of de novo pouch Crohn's disease after restorative proctocolectomy affect ileal pouch retention? *Dis Colon Rectum*. 2014;57:76–82.
176. Garrett KA, Remzi FH, Kirat HT, Fazio VW, Shen B, Kiran RP. Outcome of salvage surgery for ileal pouches referred with a diagnosis of Crohn's disease. *Dis Colon Rectum*. 2009;52:1967–1974.
177. Wu XR, Kiran RP, Remzi FH, Katz S, Mukewar S, Shen B. Preoperative pelvic radiation increases the risk for ileal pouch failure in patients with colitis-associated colorectal cancer. *J Crohns Colitis*. 2013;7:e419–e426.
178. Shen B, Fazio VW, Remzi FH, Lashner BA. Clinical approach to diseases of ileal pouch-anal anastomosis. *Am J Gastroenterol*. 2005;100:2796–2807.
179. Karoui M, Cohen R, Nicholls J. Results of surgical removal of the pouch after failed restorative proctocolectomy. *Dis Colon Rectum*. 2004;47:869–875.
180. Lavryk O, Remzi FH, Aytac E, Ashburn JH, Dietz DW, Church JM. Redo ileal pouch anal anastomosis after a failed pouch in patients with Crohn's disease: is it worth trying? *J Am Coll Surg*. 2016;223:e10.
181. Aytac E, Dietz DW, Ashburn J, Remzi FH. Is conversion of a failed IPAA to a continent ileostomy a risk factor for long-term failure? *Dis Colon Rectum*. 2019;62:217–222.
182. Aytac E, Dietz DW, Ashburn J, Remzi FH. Long-term outcomes after continent ileostomy creation in patients with Crohn's disease. *Dis Colon Rectum*. 2017;60:508–513.
183. Gomez-Senent S, Barreiro-de-Acosta M, Garcia-Sanchez V. Enterocutaneous fistulas and Crohn s disease: clinical characteristics and response to treatment. *Rev Esp Enferm Dig*. 2013;105:3–6.
184. Hawker PC, Givel JC, Keighley MR, Alexander-Williams J, Allan RN. Management of enterocutaneous fistulae in Crohn's disease. *Gut*. 1983;24:284–287.
185. Orangio GR. Enterocutaneous fistula: medical and surgical management including patients with Crohn's disease. *Clin Colon Rectal Surg*. 2010;23:169–175.
186. Taggarshe D, Bakston D, Jacobs M, McKendrick A, Mittal VK. Management of enterocutaneous fistulae: a 10 years experience. *World J Gastrointest Surg*. 2010;2:242–246.
187. Tonolini M, Magistrelli P. Enterocutaneous fistulas: a primer for radiologists with emphasis on CT and MRI. *Insights Imaging*. 2017;8:537–548.
188. Poritz LS, Gagliano GA, McLeod RS, MacRae H, Cohen Z. Surgical management of entero and colocutaneous fistulae in Crohn's disease: 17 year's experience. *Int J Colorectal Dis*. 2004;19:481–485 discussion 6.
189. Cougard PA, Desjeux A, Berdah S, Ezzedine S, Barthet M, Grimaud JC. Healing of anastomotic enterocutaneous fistulae due to Crohn's disease by anti-tNF-alpha antibodies. *Inflamm Bowel Dis*. 2010;16:1632–1633.
190. Agwunobi AO, Carlson GL, Anderson ID, Irving MH, Scott NA. Mechanisms of intestinal failure in Crohn's disease. *Dis Colon Rectum*. 2001;44:1834–1837.
191. Singh RR, Nussbaum JS, Kumta NA. Endoscopic management of perforations, leaks and fistulas. *Transl Gastroenterol Hepatol*. 2018;3:85.
192. Ballard DH, Erickson AEM, Ahuja C, Vea R, Sangster GP, D'Agostino HB. Percutaneous management of enterocutaneous fistulae and abscess-fistula complexes. *Dig Dis Interv*. 2018;2:131–140.
193. Ma C, Parker CE, Nguyen TM, Khanna R, Feagan BG, Jairath V. Identifying outcomes in clinical trials of fistulizing Crohn's disease for the development of a core outcome set. *Clin Gastroenterol Hepatol*. 2019;17:1904–1908.
194. Amiot A, Setakhr V, Seksik P, et al. Long-term outcome of enterocutaneous fistula in patients with Crohn's disease treated with anti-TNF therapy: a cohort study from the GETAID. *Am J Gastroenterol*. 2014;109:1443–1449.
195. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132:52–65.
196. Panaccione R, Colombel JF, Sandborn WJ, et al. Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. *Aliment Pharmacol Ther*. 2013;38:1236–1247.
197. Fujiwara K, Inoue T, Yorifuji N, et al. Effect of adalimumab on an enterocutaneous fistula in patients with Crohn's disease: a case series. *Intern Med*. 2015;54:2603–2607.

198. Madarame A, Kimura H, Kunisaki R. Successful treatment with ustekinumab for enterocutaneous fistulas in Crohn's disease. *J Crohns Colitis*. 2019.
199. Yan D, Ren J, Wang G, Liu S, Li J. Predictors of response to enteral nutrition in abdominal enterocutaneous fistula patients with Crohn's disease. *Eur J Clin Nutr*. 2014;68:959–963.
200. Goyer P, Alves A, Bretagnol F, Bouhnik Y, Valleur P, Panis Y. Impact of complex Crohn's disease on the outcome of laparoscopic ileocecal resection: a comparative clinical study in 124 patients. *Dis Colon Rectum*. 2009;52:205–210.
201. Lynch AC, Delaney CP, Senagore AJ, Connor JT, Remzi FH, Fazio VW. Clinical outcome and factors predictive of recurrence after enterocutaneous fistula surgery. *Ann Surg*. 2004;240:825–831.
202. Michelassi F, Stella M, Balestracci T, Giuliante F, Marogna P, Block GE. Incidence, diagnosis, and treatment of enteric and colorectal fistulae in patients with Crohn's disease. *Ann Surg*. 1993;218:660–666.
203. Broe PJ, Bayless TM, Cameron JL. Crohn's disease: are enteroenteral fistulas an indication for surgery? *Surgery*. 1982;91:249–253.
204. Present DH. Crohn's fistula: current concepts in management. *Gastroenterology*. 2003;124:1629–1635.
205. Lee SS, Kim AY, Yang SK, et al. Crohn disease of the small bowel: comparison of CT enterography, MR enterography, and small-bowel follow-through as diagnostic techniques. *Radiology*. 2009;251:751–761.
206. Seastedt KP, Trencheva K, Michelassi F, et al. Accuracy of CT enterography and magnetic resonance enterography imaging to detect lesions preoperatively in patients undergoing surgery for Crohn's disease. *Dis Colon Rectum*. 2014;57:1364–1370.
207. Fallis SA, Murphy P, Sinha R, et al. Magnetic resonance enterography in Crohn's disease: a comparison with the findings at surgery. *Colorectal Dis*. 2013;15:1273–1280.
208. Schreyer AG, Geissler A, Albrich H, et al. Abdominal MRI after enteroclysis or with oral contrast in patients with suspected or proven Crohn's disease. *Clin Gastroenterol Hepatol*. 2004;2:491–497.
209. Herrmann KA, Michaely HJ, Seiderer J, Ochsenkuehn T, Reiser MF, Schoenberg SO. The "star-sign" in magnetic resonance enteroclysis: a characteristic finding of internal fistulae in Crohn's disease. *Scand J Gastroenterol*. 2006;41:239–241.
210. Erden A, Unal S, Akkaya HE, et al. MR Enterography in Crohn's disease complicated with enteroenteric fistula. *Eur J Radiol*. 2017;94:101–106.
211. Lee JK, Stein SL. Radiographic and endoscopic diagnosis and treatment of enterocutaneous fistulas. *Clin Colon Rectal Surg*. 2010;23:149–160.
212. Bemelman WA, Warusavitarne J, Sampietro GM, et al. ECCO-ESCP consensus on surgery for Crohn's disease. *J Crohn's Colitis*. 2017;12:1–16.
213. Grimstad T, Carlsen A, Karlsen LN. Medical management of fistulising Crohn's disease. *Tidsskr Nor Laegeforen*. 2019:139.
214. Ardizzone S, Bollani S, Manzionna G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Dig Liver Dis*. 2003;35:619–627.
215. Rosenberg JL, Levin B, Wall AJ, Kirsner JB. A controlled trial of azathioprine in Crohn's disease. *Am J Dig Dis*. 1975;20:721–726.
216. Bayless TM, Hanauer SB. *Advanced therapy of inflammatory bowel disease*. 2nd ed. Hamilton, Ontario: BC Decker, Inc; 2001.
217. de Groof EJ, Cabral VN, Buskens CJ, et al. Systematic review of evidence and consensus on perianal fistula: an analysis of national and international guidelines. *Colorectal Dis*. 2016;18:O119–O134.
218. Maggiori L, Brouquet A, Zerbib P, et al. Penetrating Crohn disease is not associated with a higher risk of recurrence after surgery: a prospective nationwide cohort conducted by the getaid chirurgie group. *Ann Surg*. 2019;270:827–834.
219. Kristo I, Stift A, Argeny S, Mittlbock M, Riss S. Minimal-invasive approach for penetrating Crohn's disease is not associated with increased complications. *Surg Endosc*. 2016;30:5239–5244.
220. Mege D, Garrett K, Milsom J, Sonoda T, Michelassi F. Changing trends in surgery for abdominal Crohn's disease. *Colorectal Dis*. 2019;21:200–207.
221. Moftah M, Nazour F, Cunningham M, Cahill RA. Single port laparoscopic surgery for patients with complex and recurrent Crohn's disease. *J Crohns Colitis*. 2014;8:1055–1061.
222. Coffey CJ, Kiernan MG, Sahebally SM, et al. Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. *J Crohns Colitis*. 2018;12:1139–1150.
223. Kono T, Ashida T, Ebisawa Y, et al. A new antimesenteric functional end-to-end handsewn anastomosis: surgical prevention of anastomotic recurrence in Crohn's disease. *Dis Colon Rectum*. 2011;54:586–592.
224. Sampietro GM, Casiraghi S, Foschi D. Perforating Crohn's disease: conservative and surgical treatment. *Dig Dis*. 2013;31:218–221.
225. Golabek T, Szymanska A, Szopinski T, et al. Enterovesical fistulae: aetiology, imaging, and management. *Gastroenterol Res Pract* . 2013;2013.
226. Taxonera C, Barreiro-de-Acosta M, Bastida G, et al. Outcomes of medical and surgical therapy for entero-urinary fistulas in Crohn's disease. *J Crohn's Colitis* . 2016;10:657–662.
227. Qiu Y, Mao R, Chen BL, et al. Systematic review with meta-analysis: magnetic resonance enterography vs. computed tomography enterography for evaluating disease activity in small bowel Crohn's disease. *Aliment Pharmacol Ther*. 2014;40:134–146.
228. Papadia C, Maffei E, Del Rio P, et al. Sensitivity and specificity of magnetic resonance enterography in the clinical management of fistulizing Crohn's disease. *Inflamm Bowel Dis*. 2013;19:1896–1903.
229. Mao R, Chen YJ, Chen BL, et al. Intra-cavitary contrast-enhanced ultrasound: a novel radiation-free method for detecting abscess-associated penetrating disease in Crohn's disease. *J Crohn's Colitis* . 2019;13:593–599.
230. Camera L, Pezzullo F, Acampora A, et al. Multi-detector CT enterography in active inflammatory bowel disease: image quality and diagnostic efficacy of a low-radiation high contrast protocol. *Clin Imaging*. 2019;58:27–33.

231. da Silva Moraes AC, de Freitas Moraes G, de Araujo ALE, et al. Abdominal ultrasonography with color Doppler analysis in the assessment of ileal Crohn's disease: comparison with magnetic resonance enterography. *Intest Res* . 2019;17:227–236.
232. Novak KL, Kaplan GG, Panaccione R, et al. A simple ultrasound score for the accurate detection of inflammatory activity in Crohn's disease. *Inflamm Bowel Dis*. 2017;23:2001–2010.
233. Maconi G, Parente F, Bianchi Porro G. Hydrogen peroxide enhanced ultrasound- fistulography in the assessment of enterocutaneous fistulas complicating Crohn's disease. *Gut*. 1999;45:874–878.
234. Chen YJ, Mao R, Xie XH, et al. Intracavitary contrast-enhanced ultrasonography to detect enterovesical fistula in Crohn's disease. *Gastroenterology*. 2016;150:315–317.
235. Holroyd DJ, Banerjee S, Beavan M, Prentice R, Vijay V, Warren SJ. Colovaginal and colovesical fistulae: the diagnostic paradigm. *Tech Coloproctol*. 2012;16:119–126.
236. Sands BE, Blank MA, Patel K, van Deventer SJ. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. *Clin Gastroenterol Hepatol*. 2004;2:912–920.
237. Lee MJ, Parker CE, Taylor SR, et al. Efficacy of medical therapies for fistulizing Crohn's disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16:1879–1892.
238. Margolin ML, Korelitz BI. Management of bladder fistulas in Crohn's disease. *J Clin Gastroenterol*. 1989;11:399–402.
239. Kraemer M, Kara D. Laparoscopic surgery of benign entero-vesical or entero-vaginal fistulae. *Int J Colorectal Dis*. 2016;31:19–22.
240. Nevo Y, Shapiro R, Froylich D, et al. Over 1-year followup of laparoscopic treatment of enterovesical fistula. *JSLS*. 2019:23.
241. de Groof EJ, Bruggeman AE, Buskens CJ, Tanis PJ, Bemelman WA. Selective use of cystogram following segmental bowel resection in patients with enterovesical fistula. *Colorectal Dis*. 2019.
242. Ferguson GG, Lee EW, Hunt SR, Ridley CH, Brandes SB. Management of the bladder during surgical treatment of enterovesical fistulas from benign bowel disease. *J Am Coll Surg*. 2008;207:569–572.
243. Bertelson NL, Abcarian H, Kalkbrenner KA, et al. Diverticular colovesical fistula: what should we really be doing? *Tech Coloproctol*. 2018;22:31–36.
244. Kirsh GM, Hampel N, Shuck JM, Resnick MI. Diagnosis and management of vesicoenteric fistulas. *Surg Gynecol Obstet*. 1991;173:91–97.
245. Walker KG, Anderson JH, Iskander N, McKee RF, Finlay IG. Colonic resection for colovesical fistula: 5-year follow-up. *Colorectal Dis*. 2002;4:270–274.
246. Hepperlen TW, Stinson W, Hutson J, Bartone FF. Epithelialization after cystotomy. *Invest Urol*. 1975;12:269–271.
247. de Moya MA, Zacharias N, Osbourne A, et al. Colovesical fistula repair: is early Foley catheter removal safe? *J Surg Res*. 2009;156:274–277.