Managing Perianal Fistula

Perianal fistulas are major sources of morbidity worldwide which often require a protracted treatment course. Most simple fistulas can be managed with fistulotomy, but surgeons should remain conservative as any amount of sphincter division may result in incontinence. Management of complex fistulas are nuanced and imaging modalities may be utilized for preoperative planning. In cases of perianal Crohn’s disease, medical and surgical treatments are evolving, but often require prerequisite sepsis control through seton placement. In this report, we review the range of classic and novel treatment strategies for perianal fistulas.

INTRODUCTION

Perianal fistula(s), anorectal fistula(s), or fistula(s)-in-ano are synonymous terms for a common anorectal disorder with an incidence of 70-96,000 cases per year amongst Americans and approximately 1.0-2.3 per 10,000 people in the European Union, although the diagnosis of perianal abscesses is likely underdiagnosed.1-4 A perianal fistula is a chronic abnormal communication between the rectum/anus and the perianal skin through an epithelialized tunnel. In this chapter, we describe the diagnosis and classification of perianal fistulas, and review the wide range of traditional and novel treatment strategies.

Pathophysiology

Over 90% of perianal fistulas are cryptoglandular in origin, meaning they develop as a sequela of an anorectal abscess.5 The proportion of patients with a clinically significant anorectal abscess who subsequently develop a fistula ranges between 20-40%, even after surgical incision and drainage.6-10 The exact pathophysiology for the formation of a perianal abscess is still unknown, but the prevailing hypothesis is that it results from the infiltration of enteric microorganisms into perianal gland channels causing inflammation and obstruction that

(continued on page 18)
perpetuate further bacterial growth.\textsuperscript{11} The infection spreads outward through soft tissue until it finds an exit through the skin surface; accordingly, anorectal abscess and perianal fistula should be considered on the same pathogenic spectrum.

Alternatively, fistulas may occur from non-cryptoglandular causes such as penetrating perineal trauma, malignancy, ischemia, or chronic inflammation such as inflammatory bowel disease. Tissue healing is a complex molecular process involving inflammatory cytokines, mesenchymal cell activity (from epithelial-mesenchymal transition), extracellular matrix building/alteration, vascularity, oxygen, and hospitable healing environments.\textsuperscript{11} Perturbations of any of these factors may predispose the patient to formation of these non-cryptoglandular fistulas. Consistent evaluation and reevaluation of these risk factors in cases of non-healing or recurrence are necessary to achieve effective and lasting fistula remission.

\textbf{Anatomy}

To understand the diagnosis and treatment options for perianal fistulizing disease, a thorough understanding of the anal sphincter complex anatomy is essential. The external anal sphincter is under voluntary control and is composed of striated muscle continuous with the puborectalis and levator ani muscles. It lays superficial, external, and “cups” the internal anal sphincter which is composed of involuntarily controlled smooth muscle, comprising 85\% of the resting anal tone.\textsuperscript{12} The internal sphincter smooth muscle is continuous with the circular smooth muscle of the rectum. Rectal distension causes involuntary relaxation of the internal anal sphincter, also known as the rectoanal inhibitory reflex, followed by a reflexive contraction of the external anal sphincter preventing accidental release of rectal contents. Fecal continence is maintained by both the internal and external anal sphincters and their autonomic interaction.

A perianal fistula is the pathologic communication between the anal canal and the skin through a narrow tunnel lined by an epithelial surface. These most commonly originate at the level of the dentate line where the squamocolumnar junction and 4-10 anal glands reside (Figure 1). The Parks’ classification system is the most widely used classification system for anal fistulas, defining the fistula anatomy based on the relationship to the anal sphincter complex (Table 1).\textsuperscript{5} While the true prevalence of each fistula type is unknown and likely varies across countries, the vast majority of fistulas are of the intersphincteric and transsphincteric varieties. Suprasphincteric

\begin{figure}[h]
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\includegraphics[width=\textwidth]{Figure1}
\caption{Perianal Fistula Tracts. Illustration of Parks’ classification in the coronal plane}
\end{figure}
Managing Perianal Fistula

and extrasphincteric fistulas are most often associated with non-cryptoglandular etiologies. The modified Parks’ classification system adapts the Parks’ classification and includes the addition of submucosal fistulas which are superficial and do not traverse any sphincter muscle. Division of these fistulas pose no risk of incontinence.

Goodsall’s rule offers some guidance to the path of the fistula. The rule states that the external opening of the fistula tract located anterior to a transverse line drawn across the anus travels in a direct straight path to the anal canal/rectum. In contrast, if the external opening is posterior to the transverse anal line, the fistulous path may be curved or unpredictable. Awareness of these tendencies are critical for treatment planning.

Epidemiology

Most perianal abscesses are diagnosed during the 4-5th decade of life and are more common in men. Independent predictors of fistulization after perianal abscess formation are female gender, age between 41-60 years, diabetes mellitus, and ischiorectal or intersphincteric location of the initial abscess. There is minimal data to suggest that anal-receptive intercourse, poor hygiene, and obesity are associated with abscess formation.

Other factors associated with anorectal abscesses and fistulas include chronic systemic inflammation such as inflammatory bowel disease (IBD), immunocompromised states such as human immunodeficiency virus, and tobacco use. Crohn’s disease (CD) is a well-known risk factor for the development of perianal disease and patients with active rectal disease are at greatest risk. Hellers, et al. estimated that 15% of those with ileocolonic CD with rectal involvement had perianal fistulas, compared with 41% with rectal-sparing colonic involvement, and 92% with both colon and rectal involvement. Younger age of CD onset and African-American race or Hispanic ethnicity also increase the risk of perianal CD.

Diagnosis

CLINICAL PRESENTATION

Frequently, a detailed history and physical examination is sufficient to diagnose an anorectal abscess. Perianal pain, swelling, erythema, and tenderness are common symptoms that occur rapidly over the course of several days to weeks. Fever is not often reported by patients.
Managing Perianal Fistula

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Table 1. Modified Parks’ Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Origin</th>
<th>Path</th>
<th>Frequency13-15</th>
</tr>
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<tbody>
<tr>
<td>Simple</td>
<td>Submucosal</td>
<td>Dentate line Submucosal, superficial to the internal and external anal sphincters</td>
<td>15%</td>
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<tr>
<td></td>
<td>Intersphincteric</td>
<td>Dentate line</td>
<td>Between the internal and external anal sphincters towards the skin</td>
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<tr>
<td>Simple if low/Complex if high</td>
<td>Transspincteric</td>
<td>Dentate line Through the internal and external anal sphincters towards the skin</td>
<td>23-58%</td>
</tr>
<tr>
<td>Complex</td>
<td>Suprasphincteric</td>
<td>Dentate line Between the internal and external anal sphincters superiorly, travelling through the puborectalis then exiting back through the levator ani towards the skin</td>
<td>2-3%</td>
</tr>
<tr>
<td></td>
<td>Extrasphincteric</td>
<td>Rectum Through the levator ani towards the skin</td>
<td>1-5%</td>
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An indurated fluctuant tender mass is seen on visual examination in a superficial abscess. A digital rectal exam often elucidates the diagnosis and clarifies the abscess location but is often not tolerated by patients without sedation or anesthesia. The differential diagnosis includes a thrombosed external hemorrhoid, fissure, pilonidal disease or hidradenitis, venereal disease, CD, or anal cancer. In these cases, inquiring about trauma or high-risk sexual practices and a thorough review of systems is paramount. A patient’s bowel habits and practices, anal sphincter function, previous anorectal surgery, and comorbidities are also key for surgical planning.

Patients with perianal fistula following treatment of anorectal abscess will typically report perianal swelling and foul-smelling drainage. The induration and pain often wax and wane as abscesses bloom then drain through the fistula. Fistulas are classified as “simple” or “complex”. A simple fistula is low (submucosal, intersphincteric, and low transspincteric) with minimal internal anal sphincter involvement and has a single fistula opening. A complex fistula is high (high transspincteric, extrasphincteric, or suprasphincteric), has multiple external openings, or exits anteriorly as a rectovaginal fistula (Figure 2). Further, complex fistulas are associated with non-cryptogenic causes such as CD or malignancy.23

Patients with spontaneous fistula following resolution of a remote anorectal abscess or recurrent fistula following treatment should undergo workup of non-cryptogenic causes. Throughout the process of diagnosis and treatment of anorectal abscesses and fistulas, revisiting and questioning the etiology is important to avoid misdiagnosis.

**IMAGING**

Most abscesses and fistulas are diagnosed by a history and physical and do not typically require imaging.24 Further detail about potential secondary abscesses or fistula tracts can be investigated during treatment and instrumentation. In cases of complicated fistulas, imaging may be useful to define anatomy and determine sphincter involvement.

A fistulogram may be helpful to evaluate a surgical reference in high transspincteric,
Managing Perianal Fistula

suprasphincteric, or extrasphincteric fistulas and may identify secondary tracts. A fistulogram is performed by inserting an 8-French foley catheter into the external fistula opening, occluding the opening with the balloon and then injecting the tract with contrast under pressure. A balloon with radiopaque fluid within the anus helps mark the puborectalis muscle and assists in determination of anal canal length. While studies report the ability to identify 75% of internal fistula openings and 92% of secondary tracts, it can be technically difficult to perform, complicated to interpret, and requires expertise. We do not routinely employ fistulography.

Computed tomography may assist in perianal abscess characterization but is of minimal value for fistulas given its inadequate soft tissue contrast resolution. Pelvic magnetic resonance imaging (MRI) provides improved diagnostic accuracy for fistulas but has limited resolution for determining internal fistula openings and cannot discern the dentate line. Its strength lies in the cross-sectional evaluation of the pelvic floor. Endoanal ultrasound is a safe, rapid, and well-tolerated examination of the pelvic floor and sphincter anatomy and allows for 3D image reconstruction. Routine use of hydrogen peroxide improves ultrasound accuracy through tiny air bubble generation, changing the fistula tract from hypoechoic to hyperechoic and enhancing contrast (Figure 3).

A prospective evaluation of endoanal ultrasound and MRI utility found that MRI was able to detect all abscesses and 4/5 fistulas in cases of simple perirectal infection. Among complicated cases (multiple recurrences or IBD-associated) 6/7 abscesses, 12/14 fistulas, but only 75% of internal fistula openings were identified. In a blinded prospective study by Schwartz, et al. endoanal ultrasound, MRI, and surgical examination were compared and all were at least 85% accurate for assessment of perianal fistulas, but accuracy increased to 100% when any two methods were combined. In situations where MRI or endoanal ultrasound are not accessible, transperineal ultrasound is a cheap, non-invasive, and rapid tool with comparable accuracy to endoanal ultrasound for abscess and fistula detection, but provides lower resolution of the anal sphincter and cannot perform 3D reconstruction.

While neither pelvic MRI nor endoanal ultrasound is perfect, we advocate for the use of an imaging modality when dealing with complicated fistulas.

**Treatment**

In cases of a perianal abscess or fistula with associated abscess, surgical incision and drainage should be performed within 24 hours to limit the risk of deep infection or sepsis, particularly in patients with diabetes or who are immunocompromised. Abscess aspiration is not recommended given its 41% failure rate. Incisions should be left open to heal by secondary intention, and additional antibiotics after sufficient drainage have not been shown to affect abscess healing or recurrence rate.

The use of post-drainage antibiotics for prevention of fistula formation is debated. One placebo-controlled randomized trial from 2011 showed no effect of 10 days of amoxicillin-clavulanic acid on rates of fistula formation but another more...
recent single-blind randomized trial showed that 7 days of oral metronidazole and ciprofloxacin after abscess drainage yielded a protective effect against fistula development, with an odds ratio of 0.37 (95% CI 0.2-0.7). It is our practice to omit adjuvant antibiotics.

In determining the optimal treatment for perianal fistulas, it is best to first classify the fistula anatomically and determine whether the fistula is “simple” or “complex” as defined in the previous section, DIAGNOSIS – CLINICAL PRESENTATION. Both diagnosis and treatment are best accomplished with an anorectal exam under anesthesia, and preoperative imaging is recommended in cases of suspected or confirmed complex fistulas or recurrent fistulas. The primary goal of the initial exploration is to define the fistula and control sepsis by placing a non-cutting seton. A seton prevents recurrent abscesses and may be kept long term (months to years) without negative consequences, allowing for sepsis or unfavorable clinical factors such as active proctitis to quiesce before attempted fistula repair. Cutting setons are not recommended due to their risk of sphincter damage and anal deformation.

A fistulotomy involves incising the fistula and debriding the epithelialized tract. Incontinence rates range from 0-64% and increases with greater division of the external anal sphincter. Thus, surgeons should remain conservative. A fistulotomy should still be considered the gold-standard approach given that the majority of cryptoglandular fistulas are not complicated and involve a minimal amount of sphincter. In a single-center study of 675 patients with fistulas involving less than one third of the external anal sphincter by preoperative MRI, fistula healing was achieved in 98% of patients after a single fistulotomy, and in 2% after repeat fistulotomy, without any change in continence scores.

For certain circumstances or complex fistulas, a variety of sphincter-preserving operations are available. Endorectal advancement flap is performed by mobilizing a rectal tissue flap of mucosa and submucosa to cover the fistula’s internal opening, leaving the sphincter complex intact. This can only be performed on single tracts in the absence of proctitis with success rates ranging from 45-93%. The procedure for ligation of the intersphincteric fistula tract (LIFT) was first described by Rojanasakul, et al. in 2007 as a sphincter preserving procedure with 94% effectiveness. The technique involves the ligation and removal of the fistula pathway through the intersphincteric space (Figure 4). The majority of reports on this topic are retrospective small series.
Managing Perianal Fistula

In studies including patients with transphincteric fistulas exclusively, healing rates range from 61-100%. Mushaya, et al. compared LIFT to an anorectal advancement flap in the treatment of cryptogenic complex transphincteric fistulas and found similar recurrence rates (8%), but LIFT allowed patients to return to normal activities one week earlier.

Other sphincter preserving techniques include the insertion of a fistula plug or fibrin glue injections. An anal fistula plug is made of lyophilized porcine intestinal submucosa and is meant to provide a scaffold for host fibroblasts to promote healing after implantation into the fistula tract. Fibrin glue promotes clot development which induces fibrinolysis and tissue-healing processes. Success rates of both vary widely in the literature and follow-up studies of both techniques have failed to replicate initial success. Usage of both of these techniques have largely fallen out of favor due to poor efficacy.

Complex Fistula Treatment

The treatment of complex anorectal fistulas is nuanced and challenging. Routine use of imaging, including endoanal ultrasound and pelvic MRI, is advised for the majority of suprasphincteric and extrasphincteric fistulas. Anorectal manometry is useful as an assessment of baseline function or when addressing a high transsphincteric fistula. Fistulotomy with sphincteroplasty is a surgical option which attempts to reconstruct incised sphincter muscle to reduce the risk of incontinence. Recent studies on its usage in complex perianal fistulas have shown promise, but no randomized trials exist. Careful patient selection to avoid patients with any sphincter involvement must be exercised to prevent incontinence.

The body of literature surrounding medical and surgical treatment of Crohn’s-related perianal fistulas has grown significantly over the past decade. The cornerstone of effective fistula management has been concomitant medical and surgical therapy. Anti-tumor necrosis factor alpha (anti-TNF) therapy [i.e. infliximab (IFX) or adalimumab (ADA)] is considered the most effective class of medical therapy, inducing complete fistula healing in 55% of patients receiving IFX and 60% receiving ADA. The use of ciprofloxacin has been trialed as monotherapy, and when given in combination with ADA has been shown to improve symptoms and fistula healing rates by 24%. Despite these promising results, anti-TNFs and antibiotic therapy are most efficacious after surgical management of abscesses and sepsis through seton placement.

Even in CD, fistulas are most often treated with fistulotomy provided the anal sphincter complex is not significantly involved. Previously discussed sphincter-sparing surgical options are also efficacious but should only be attempted in the absence of proctitis. An emerging tool for fistula management in perianal CD is the injection of mesenchymal stem cells (MSCs). The recently completed ADMIRE-CD phase III clinical trial utilized allogeneic expanded adipose-derived MSCs (Cx601-darvadstrocel) in which 120 million MSCs were injected around the internal fistula opening and peri-fistula tissue along tract walls. A total of 212 patients received Cx601 or saline placebo and the trial found that significantly more patients achieved both clinical closure of external fistula openings and absence of collections on imaging in the experimental arm. These results were redemonstrated at 52-weeks, with 59% in the Cx601 group maintaining clinical remission. Recently, the phase-1 STOMP trial also studied the application of autologous MSCs on a fistula plug. Twelve patients with cryptoglandular fistulas were treated with 83% success at six months. The advent of novel stem cell technology in the treatment of complicated perianal fistulas shows promise alongside improving medical and surgical therapy.

Fecal diversion and proctectomy are aggressive but effective last-resort treatment options for refractory perianal fistulizing disease, particularly in CD. Galandiuk and colleagues report 62% of patients with perianal CD will require fecal diversion at some point in their life. For patients requiring temporary fecal diversion, over 40% ultimately require proctectomy. Thus, a comprehensive discussion setting expectations with patients is recommended early after diagnosis.

In cases of fistulas associated with malignancy or involving other pelvic organs, a multidisciplinary approach is recommended. Consideration of tissue viability and potential radiation effects is particularly important in cases requiring reconstruction.
CONCLUSION

Perianal fistulating disease is a major source of morbidity and its diagnosis and treatment are challenging. Vigilance should be exercised to avoid misdiagnosis of non-cryptoglandular fistulas, particularly in cases of recurrent, non-healing, or complicated fistulas. In these cases, use of multiple imaging modalities allows a more thorough understanding of anatomy, yet nothing replaces early examination under anesthesia as the gold-standard for both diagnosis and therapy. The highest priorities when treating perianal fistulizing disease are determining whether the fistula is simple or complicated and controlling sepsis. Fistulotomy is an effective treatment for most simple fistulas, even Crohn’s-related fistulas, but surgeons should remain conservative as any anal sphincter division risks incontinence. Patients with complicated fistulas or Crohn’s disease should be evaluated with a multidisciplinary approach to optimize medical and surgical interventions. Emerging stem cell therapies are minimally-invasive, sphincter-preserving, and offer promising results.

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References

Managing Perianal Fistula

DISPATCHES FROM THE GUILD CONFERENCE, SERIES #42

(continued from page 24)


38. Garg P. Is fistulotomy still the gold standard in present era and is it highly underutilized?: An audit of 675 operated cases. *Int J Surg.* 2018;56:26-30. doi:10.1016/j.ijsu.2018.06.009


43. van Onkelen RS, Gosselin MP, Schouten WR. Is it possible to improve the outcome of transanal advancement flap repair for high transsphincteric fistulas by additional ligation of the intersphincteric fistula tract?. *Dis Colon Rectum.* 2012;55(2):163-166. doi:10.1097/DCR.0b013e31823e0f74


50. Hirschburger M, Schwanndner T, Hecker A, Kierer W,
Managing Perianal Fistula

DISPATCHES FROM THE GUILD CONFERENCE, SERIES #42


57. 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(2):98-103. doi:10.1097/01.slb.0000063862.67320.6f


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