Perianal Fistulas

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Abstract: Perianal fistulas are a chronic, debilitating disease that requires lifelong monitoring and, potentially, lifelong treatment. Lesions are characterized by ulcerations with draining fistulous tracts around the anal region. Most dogs experience significant pain and discomfort with this condition. Bacterial infections are a frequent secondary problem. Definitive diagnosis is based on clinical signs, signalment, history, and a thorough examination. The most successful treatment is immunomodulatory therapy (cyclosporine with or without ketoconazole and topical tacrolimus). Perianal fistulas can be difficult to treat, frustrating both veterinarians and owners.

Case Presentation

Buddy, a 6-year-old, neutered, mixed-breed dog weighing 81.4 lb (37 kg), presented with a 30-day history of tenesmus and dyschezia. Buddy had been diagnosed with perianal fistulas 1 year previously. The fistulas were mild in severity, and the owner chose to treat with topical tacrolimus, which was applied to the perianal region once daily for approximately 6 months. This therapy was discontinued when the lesions resolved. When the lesions reappeared, the owner resumed the therapy. Initially, Buddy responded to the resumed therapy, but over the 30 days prior to presentation, the lesions and clinical signs had worsened. Due to lack of perceived efficacy, the owner discontinued the tacrolimus. There was no history of other medical issues, and Buddy was up-to-date on all vaccinations.

Physical Examination Findings and Initial Diagnostics

A diagnosis of perianal fistulas is usually made based on signalment, clinical signs, history, and physical examination findings. It is very important to distinguish perianal fistulas from other diagnostic differentials, such as chronic anal sac abscessation with secondary fistulas, colitis, aggressive perianal tumors (i.e., adenocarcinoma), caustic injury, and untreated bite wounds.1 On presentation, Buddy was very painful in the perineal area and periodically licked his anus. The perianal area was moist and erythematous, and ulcerations and fistulous draining tracts were present circumferentially around the anus.

Buddy was sedated with medetomidine (Dexdomitor, Pfizer), and a thorough perianal and rectal examination was performed. Palpation revealed no thickening of the anal sacs. Numerous fistulous draining tracts covered about 270° of the circumference of the anus and ranged from about 1 to 2 mm in depth (FIGURE 1). None of the fistulous tracts communicated with the colon. Rectal examination results were normal. Cytology of the fistulous tracts was performed and revealed numerous extracellular and intracellular cocci bacteria and neutrophils. A complete blood count (CBC) and serum chemistry panel were conducted, and the results were within normal limits.

Treatment

The secondary bacterial infection was treated with cephalixin (26.7 mg/kg PO bid) for 30 days. For additional immunomodulatory therapy to address the perianal fistulas, Buddy was treated with cyclosporine (Atopica, Novartis; 4 mg/kg PO bid) until recheck. A 1-month recheck examination was scheduled with the owner.

Recheck

At Buddy’s follow-up examination 30 days after starting treatment, the perianal tissue appeared normal, with no active perianal fistulas present (FIGURE 2). A digital rectal examination was performed with no sedation needed, and no abnormalities were palpated. The owner reported that all clinical signs had resolved. At this time, because the patient was no longer painful in the perineal area, topical tacrolimus was restarted, to be applied to the perineal area twice daily.

Because the lesions had resolved, tapering of the cyclosporine therapy was initiated. There are multiple ways to taper cyclosporine therapy; we prefer to taper gradually. A typical tapering schedule was used for Buddy, with follow-up visits scheduled monthly to assess for any flare of lesions. First, the cyclosporine dosage was reduced from 4 mg/kg bid 7 d/wk to 4 mg/kg bid 5 d/wk (i.e., skipping Wednesday and Sunday). At the first 1-month follow-up examination, Buddy continued to do well; therefore, the dosage was further reduced to 4 mg/kg bid every other day for a total of 4 weeks. At the next follow-up, the dosage was to be reduced to twice weekly for 4 weeks, then to once weekly for 4 weeks. If the lesions had not recurred after 4 months, the cyclosporine would be discontinued.

Tacrolimus therapy was to be maintained at topical application twice daily for 4 weeks after cyclosporine discontinuation. If no lesions were noted at that time, the tacrolimus would be decreased...
Perianal Fistulas

Perianal fistulas, also known as anal furunculosis, can be a chronic, progressive, debilitating disease of the perianal tissue. The disease is characterized by ulcerative, painful, malodorous lesions due to the local tissue destruction and secondary infection.1 Dogs can present with a single or numerous draining tracts; in some cases, the anus may be completely surrounded.

Pathogenesis

The complete pathogenesis of perianal fistulas is unknown, but several theories exist as to the underlying cause, which is likely complex and multifactorial. Originally, it was thought that the most important factors in the disease were anatomic characteristics such as (1) a broad-based tail, (2) low tail carriage, and (3) increased density of apocrine sweat glands in the zona cutanea, the cutaneous region surrounding the anal canal.3 More recently, an immune-mediated basis has been suggested due to a favorable response to treatment with immunosuppressive or immunomodulatory medications such as prednisone, azathioprine, cyclosporine, and tacrolimus.2–4 Humans develop a similar condition that has been linked to food allergy,1 and it is thought that there is a strong correlation between perianal fistulas, colitis, and food allergy in dogs as well.5 The pathogenesis of perianal fistulas also likely has a genetic association; most affected dogs are German shepherds. Research has revealed that German shepherds with the DLA-DRB1*00101 allele have a five times greater risk of developing perianal fistulas than German shepherds not expressing this allele.6

Signalment

Perianal fistulas are most frequently reported in German shepherds, with reports stating that this breed comprises as many as 84% of affected dogs.7 Other breeds that have been reported to be affected include Irish setters, collies, Border collies, Old English sheepdogs, Labrador retrievers, English bulldogs, beagles, Bouvier des Flandres, spaniels, and mixed breeds.7 There is no definitive sex predilection, but the condition is more common in middle-aged dogs, with a mean age of 4 to 7 years.7

Clinical Signs and Diagnosis

Owners most commonly report clinical signs such as dyschezia, tenesmus, hematochezia, constipation or obstipation, diarrhea, ribbon-like stool, increased frequency of defecation, purulent perianal discharge and/or bleeding, perianal licking, self-mutilation, perianal pain, scooting, offensive odor, low tail carriage, and weight loss (BOX 1). In general, the diagnosis of perianal fistulas is made based on signalment, clinical signs, history, and physical examination findings.1 However, one study revealed that 50% of patients with perianal fistulas had a concurrent histopathologic diagnosis of colitis.4 Because colitis and perianal fistulas exhibit very similar clinical signs, if clinical signs of both are present, colonoscopy and biopsies may be necessary to make a complete diagnosis.5

Perianal fistulas may also extend to involve the anal sacs. Anal sac involvement can make treatment of perianal fistulas very difficult, with a high rate of recurrence. A thorough rectal examination is needed to assess for anal sac involvement.7

Figure 1. Perianal fistulas (arrows) before initiation of antibacterial and immuno-modulatory therapy.

Figure 2. The same dog as in Figure 1 after 30 days of treatment with cyclosporine. No active perianal fistulas are present.
**Box 1. Clinical Signs of Perianal Fistulas**

- Tenesmus
- Dyschezia
- Hematochezia
- Constipation or obstipation
- Diarrhea
- Ribbon-like stool
- Increased frequency of defecation
- Purulent perianal discharge
- Self-mutilation
- Perianal pain
- Scooting
- Offensive odor
- Low tail carriage
- Weight loss

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**Box 2. Medical Therapy for Perianal Fistulas**

### Immunosuppressive or Immunomodulatory therapy

- **Induction**
  - Cyclosporine: 4 to 8 mg/kg PO total daily dose until resolution of fistulas
  - Cyclosporine and ketoconazole: cyclosporine starting at 0.5 mg/kg PO bid to 5 mg/kg daily and ketoconazole at 5 to 7.5 mg/kg PO daily to bid
  - Tacrolimus: apply a small amount to the affected area q12h
  - Prednisone: 2 mg/kg PO daily until resolution of lesions, tapered to 1 mg/kg PO every other day
  - Azathioprine: 2 mg/kg PO daily until resolution of lesions, tapered to 1 mg/kg PO every other day

- **Maintenance**
  - Cyclosporine with or without ketoconazole: lowest frequency of daily dosing that keeps lesion in remission; discontinue if possible
  - Tacrolimus: apply a small amount to the affected area q48–72h
  - Prednisone: 0.5 to 1 mg/kg every other day; discontinue if possible
  - Azathioprine: 1 mg/kg q48–72h; discontinue if possible

### Dietary therapy

- Novel-protein diet
- Hydrolyzed diet

### Hygiene therapy

- Clip and cleanse the area
- Keep the area dry and clean
- Administer antibiotic therapy

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**Treatment**

**Surgical Management**

Reported therapies include surgical and medical management options. Surgical techniques focus on removal of the diseased tissue and destroying the epithelial lining to prevent recurrence. Surgical methods for achieving this include excision, chemical cauterization, cryotherapy, deroofing and fulguration, and laser excision. The success rate varies from 48% to 100% based on the method; however, historically, the overall recurrence rate approaches 70%. Surgical complications are common, with anal stenosis reported in up to 15% of cases and fecal incontinence reported in up to 27% of cases. Presurgical immunosuppressive and antibacterial therapy followed by surgical removal of residual draining tracts, cryptectomy, and bilateral anal sacculectomy produced clinical resolution in 84% of 25 dogs followed up for 8 to 32 months. In another study, five dogs that received anal sacculectomy, excision of residual fistulas, and pre- and postsurgical treatment with azathioprine and metronidazole had 100% resolution with a 7- to 10-month follow-up.

En bloc excision of diseased tissue and bilateral anal sacculectomy in 51 dogs followed for 1.5 to 36 months achieved acceptable results in 64% of cases. Reported postsurgical complications included fistula recurrence, fecal incontinence, stricture formation, and dehiscence in 2%, 4%, 13%, and 14% of patients, respectively. In another study, surgery was combined with a novel-protein diet and preoperative and postoperative medical immunosuppressive or immunomodulatory therapy in 33 dogs; complete resolution was reported in 83% to 100% of these cases up to 1 year postoperatively. Reported postsurgical complications were similar to those in other studies, including intermittent licking, diarrhea, constipation, tenesmus, and decreased anal tone on digital examination, and were observed in up to 20% of dogs.

**Medical Management**

Given the high rate of recurrence and potentially serious complications with surgery, many clinicians choose medical management as first-line therapy for perianal fistulas. Anal sacculectomy is recommended if the anal sacs are involved; whether normal anal sacs should be removed is a matter of debate. However, for cases of perianal fistulas with concurrent anal sacculitis, surgery may be needed to remove affected anal sacs if medical therapy alone is not effective.

**Pharmacologic agents**

The first aspect of medical management is immunosuppressive or immunomodulatory therapy. There are two phases: (1) the induction phase (i.e., resolving clinical signs) and (2) the maintenance phase (i.e., keeping clinical signs in remission). The most common medications used during the induction phase include cyclosporine with or without ketoconazole, glucocorticoids, azathioprine, and topical tacrolimus. Prednisone is not our first choice because its efficacy is lower that that of cyclosporine therapy. A 2005 study revealed that prednisone completely resolved 33% of fistulas, with partial resolution in another 33% of patients. Recommended prednisone protocols include 2 mg/kg PO daily until lesions are in remission, then tapering down to maintenance doses of 0.5 to 1 mg/kg PO every other day. The most common side effects of prednisone therapy are polyuria, polydipsia, and polyphagia.

Azathioprine has also been used successfully in perianal fistula therapy. Azathioprine takes about 2 to 3 weeks to reach optimal blood levels, so treating concurrently with prednisone at the dosage...
recommended above is advised. The recommended dosage of azathioprine is 2 mg/kg PO daily until remission of fistulas is achieved; the dosage is then decreased to 2 mg/kg every other day and then to maintenance doses of 1 mg/kg PO every other day. In one study of 14 dogs treated with azathioprine and prednisone, about 64% of dogs had complete or partial remission. Routine CBCs and serum chemistries are needed to monitor for myelosuppression and liver toxicity. Myelosuppression is reported to be the most common adverse effect of azathioprine therapy and can resolve in some dogs with dosage reduction.

The most successful medical therapy used recently, and our first choice, is cyclosporine. Cyclosporine, a calcineurin inhibitor, is an immunomodulating drug that primarily works by inhibiting interleukin-2 transcription, which prevents the activation and proliferation of T lymphocytes. One study showed a 96% reduction in perianal fistulas with this medication; 69% of dogs had complete resolution, 27% had partial resolution, and only 4% showed no improvement. However, more than one-third of dogs had recurrence of the lesions within 2 to 3 months. This study treated with cyclosporine only until 2 weeks past clinical resolution or until no further improvement was apparent. Several studies report resolution of clinical signs in up to 100% of dogs and clinical remission in up to 93% of dogs.

When cyclosporine is being used as the sole therapy, the initial total daily dose is 4 to 8 mg/kg, administered until lesions are no longer present. To prevent recurrence, we recommend transitioning to maintenance therapy, as outlined for Buddy. Once all lesions of perianal fistula disease are in remission, cyclosporine therapy can be tapered. There are several options for tapering cyclosporine; we favor a slow reduction in the number of doses per week, keeping the same total daily dose, which can be split twice daily or given once daily. Over 3 to 5 months of tapering, the goal is to discontinue cyclosporine with concurrent use of tacrolimus. Some patients continue to require cyclosporine, but generally at less than daily administration.

Controversy exists about whether cyclosporine levels require monitoring. The recommended trough levels of cyclosporine in dogs are based on data established for humans and animals receiving organ transplants. A relationship has not been established between cyclosporine trough concentrations and efficacy of treatment for perianal fistulas. Adverse effects of cyclosporine therapy include primarily gastrointestinal signs (vomiting, soft stool, or diarrhea); chronic effects can include gingival hyperplasia and hirsutism. Rare reported adverse effects of cyclosporine are papillomatosis, atypical bacterial or fungal infections, and psoriasisform dermatitis.

Ketoconazole can be added to cyclosporine therapy to decrease the dose of cyclosporine needed and the associated cost of therapy. Ketoconazole competitively inhibits cytochrome P450 3A enzyme, resulting in a prolonged serum half-life of cyclosporine.

Recommended dosage protocols for combination therapy with cyclosporine and ketoconazole include doses of cyclosporine ranging from 0.5 mg/kg PO bid to 5 mg/kg PO daily and doses of ketoconazole ranging from 5 to 7.5 mg/kg PO daily to bid. Combining protocols of cyclosporine and ketoconazole are estimated to decrease the cost of therapy by up to 70% with no change in efficacy compared with cyclosporine alone. Adverse effects of ketoconazole include gastrointestinal signs (anorexia, vomiting, and diarrhea), hepatotoxicity, thrombocytopenia, and skin reactions, including pruritus and alopecia. At higher doses of ketoconazole and cyclosporine, adverse effects such as transient vomiting and decreased appetite have been observed; these effects resolved when the doses were decreased.

Tacrolimus is a topical calcineurin inhibitor with a mechanism of action similar to that of cyclosporine. In one study of 10 dogs that used tacrolimus as the sole therapy for perianal fistulas, significant clinical improvement was seen in nine dogs, five of which had clinical resolution. In another study that used tacrolimus in conjunction with prednisone, a novel-protein diet, and a short course of metronidazole, there was complete resolution in 87% of dogs without relapse over a 2-year period. The 2-year period, tacrolimus was applied as needed to control lesions (every 1 to 7 days); 73% of the dogs continued on the novel-protein diet, and 33% received prednisone intermittently to every 48 hours. Tacrolimus may be most suitable as a long-term maintenance therapy applied every 24 to 72 hours to prevent clinical signs and fistula recurrence. Tacrolimus therapy can be initiated once the severity of the disease has subsided and the perineal area can be treated topically by the owner. It can also be considered as initial therapy for mild lesions. Recurrence of disease is common (about 50% of cases) after cessation of therapy.

**Dietary therapy**

The second aspect of medical management to consider is dietary therapy. Due to the strong correlation and similarities with colitis, some recommend a dietary change to a novel-protein or hydrolyzed-protein diet. In one study, there was a lower recurrence rate after surgical excision of diseased tissue and bilateral anal sacculectomy when dogs also received a novel-protein fish and potato diet. The lower incidence of recurrence was attributed to the dietary change. We generally recommend changing to a novel-protein diet during the maintenance phase of medical therapy, especially if lesions recur as the oral medications are tapered.

**Hygiene therapy**

The third aspect of medical management involves keeping the perineal area clean and free of secondary bacterial infection. Hygiene therapy involves clipping and cleaning, regional moisture reduction, and antibiotic therapy based on culture and susceptibility results. Empirical antibiotic therapy can consist of metronidazole, cephalixin, cepfodoxime, or amoxicillin–clavulanate; however, refractory infections are best treated based on culture and susceptibility testing. Adjunctive topical antibiotic therapy...
with mupirocin ointment can be useful if the patient can tolerate topical application.7

**Conclusion**

Perianal fistulas can be a difficult disease to manage due to the high recurrence rate with most therapies, leading to a potentially guarded prognosis. At this time, the most efficacious treatment is cyclosporine with or without ketoconazole, with the addition of tacrolimus as a long-term maintenance therapy to help prevent relapse. If there is any anal sac involvement, surgical removal of the anal sac may be needed after initially treating with immunosuppressive or immunomodulatory therapies. In addition, a novel-ingredient food trial may help control this disease.

**References**