

Dermclub 1, 2006: Managing Anal Furunculosis in Dogs

INTRODUCTION

- Canine anal furunculosis (perianal fistula) is a chronic, painful, progressive inflammatory and ulcerative disease associated with the perianal, anal, and/or perirectal tissues.
- The disease is characterized by the presence of focal or multifocal, dissecting ulcerative sinus tracts of varying diameter, depth, and connectivity developing in the perianal tissue which can extend 360° circumferentially around the anus.
- Canine anal furunculosis has a clinical appearance similar to that of perianal fistula in humans, which is often associated with granulomatous enteritis (Crohn's disease).

SIGNALMENT AND CLINICAL SIGNS

- **German shepherds** with this disease appear to be overrepresented, with one report showing that 84% of affected dogs were German shepherds. Other breeds reported include Irish setters, Collies, Border collies, Old English sheepdogs, Labrador retrievers, English bulldogs, Beagles, Bouvier des Flandres, Spaniels, and mixed breeds.
- The disease usually affects **middle-aged dogs** with a mean age of 4 to 7 years with no sex predilection.
- Clinical signs associated with anal furunculosis are listed below.

Clinical signs of anal furunculosis

- Tenesmus
- Dyschezia
- Haematochezia
- Constipation or obstipation
- Diarrhea
- Ribbon like stool
- Increased frequency of defaecation
- Perianal purulent discharge and/or bleeding
- Perianal licking
- Self mutilation
- Perianal pain
- Scooting
- Offensive odour
- Low tail carriage
- Weight loss

PATHOGENESIS

- A definitive cause of anal furunculosis has not been described; however, many theories have been proposed.
- The older hypotheses include **poor conformation** of the perianal region and tail (broad-based low tail carriage), **anal crypt faecalith** impaction resulting in abscessation, spread of **infection** from the anal glands or anal sacs, **trauma**, and **foreign body reaction**. Unfortunately, little evidence supports any of these hypotheses.
- The current theory involves a multifactorial **immune-mediated disease** process. An immune-mediated process is suspected because both canine anal furunculosis and Crohn's disease respond to immunomodulation. Accumulating evidence shows that Crohn's disease is the result of an unbalanced host immune response to intestinal triggers in genetically susceptible humans. Because German Shepherds with canine anal furunculosis also have clinical and histologic evidence of colitis (inflammatory bowel disease [IBD]), it is possible that enteral triggers (dietary antigens, bacterial antigens, superantigens) are initiators of canine anal furunculosis as well.

PHYSICAL EXAMINATION

- Examination of the perianal area of patients with anal furunculosis usually requires **sedation or general anaesthesia** because of severe pain.
- **Clipping** the perianal region is often necessary to assess the severity of disease. Lesions may vary from superficial pinpoint tracts to large ulcerated areas. Several of these tracts may often be interconnected. Tracts may tunnel deep within the surrounding tissue and occasionally communicate with the rectum, anus, and/or anal sacs.
- The tracts should be **probed** with a **sterile, blunt instrument** to determine their extent and involvement with regional structures.
- A **rectal examination** should be performed to assess the **external anal sphincter, anal sacs, and rectal mucosa**. Thickening (i.e., fibrosis) of the anus and rectum can be palpated during the rectal examination. It is important to determine whether there is **evidence of anorectal stenosis** and/or **perineal hernia**, which would affect the prognosis. The **anal sacs** may be normal, impacted, or ruptured. In addition, the anal sacs may be incorporated within surrounding tissue fibrosis.
- **Cannulation of the anal sac ducts** determines whether they are occluded. **Flushing the anal sacs** with sterile saline may reveal a previously unobserved fistulating tract.

- The primary **differential diagnoses** include anal sac abscessation, perianal adenoma, anal sac adenocarcinoma, anal squamous cell carcinoma, rectal neoplasia, atypical bacterial infection, mycosis, and oomycosis (pythiosis, lagenidiosis).

DIAGNOSTIC EVALUATION

- The diagnosis of canine anal furunculosis is based on history, physical examination findings, and ruling out other primary diagnostic differentials.
- Superficial **cytology** is a standard tool for evaluating the cutaneous and sinus tract microenvironment. It invariably reveals **pyogranulomatous inflammation** with a mixed bacterial population.
- **Fine-needle aspiration** of an enlarged anal sac is warranted to rule out abscessation or neoplasia.
- **Sinus tracts** should be **cultured** with a **sterile swab** or **tissue biopsy** for **bacterial culture and susceptibility testing** because controlling secondary infection with antibiotics may take weeks to months.
- **Tissue biopsy for histopathology** can be used to verify the tentative diagnosis of canine anal furunculosis and to rule out neoplasia. Biopsy sites often have to heal by second intention.
- Other **diagnostics** that may prove useful include colonoscopy with biopsy, and pelvic radiography.

MANAGEMENT

SURGICAL

- Primary surgical treatment of canine anal furunculosis was previously advocated. Surgical procedures involved either destroying the epithelial lining of sinus tracts or total en bloc tract excision to remove diseased tissue and prevent recurrence.
- Surgical treatment included surgical excision, chemical cauterization, cryotherapy, derroofing and fulguration, and laser (i.e., neodymium: yttrium aluminum garnet) excision. Tail amputation was also recommended as a means of reducing faecal soiling and contamination over the perianal area.
- These procedures reportedly had varying success rates (48% to 97% of cases) but a high rate of recurrence of disease (approximately 70%), with some surgical techniques necessitating further surgical treatments.

- Other frequent serious complications such as **anal stenosis** (up to 15% of cases, with the incidence approaching 47% following cryotherapy) and **faecal incontinence** (in up to 29% of cases) were reported.

MEDICAL

- Fortunately, medical management in recent years has shed new light on this devastating disease. Several studies have reported favourable results with **immunosuppressive** or **immunomodulating** drug regimens, including **cyclosporin**, **tacrolimus**, and **azathioprine** and **metronidazole**. Conventional immunosuppression with glucocorticoids has also been reported, albeit without the same level of success.
- Consequently, clinicians can now give their clients new therapeutic options that can positively affect the prognosis. It is paramount for clinicians to discuss with clients the **goal, effectiveness, length, and cost of therapy** before implementing it.
- It is important for owners to understand that canine anal furunculosis is a chronic relapsing and remitting disease that can be managed but not necessarily cured. Lifelong therapy may be required as with other immune-mediated diseases. If one drug combination does not achieve the defined goal, another drug protocol is warranted.
- The **first goal of therapy** should be to **alleviate large bowel clinical signs** such as tenesmus, dyschezia, hematochezia, constipation or obstipation, diarrhea, ribbon-like stool, increased frequency of defecation, and perianal pain. The **second goal of therapy** should be to **reduce the diameter, depth, extent, and recurrence of sinus tracts**.
- **Medical management** comprises **immunosuppressive or immunomodulatory treatment** as well as **hygiene**, and **antimicrobial therapy**.
- As with treating other immune-mediated diseases, immunosuppressive therapy consists of **induction** and **maintenance** phases. The **induction phase** usually consists of oral systemic therapy to alleviate clinical signs associated with pain and inflammation. This phase can last 8 to 20 weeks.
- Once signs of pain and lesional skin have improved, **maintenance therapy** should be initiated. It may consist of the lowest effective dose of oral therapy administered during induction and/or topical therapy. Clinicians should not prescribe topical therapy until owners can apply it safely and without discomfort to their dogs.

IMMUNOSUPPRESSIVE OR IMMUNOMODULATORY THERAPY: INDUCTION GLUCOCORTICOIDS, AZATHIOPRINE AND METRONIDAZOLE

- Glucocorticoids have reportedly been used to treat canine anal furunculosis.

Association of perianal fistula and colitis in the German Shepherd dog: response to high-dose prednisolone and dietary therapy. JAAHA 32:515-520, 1996

Prednisolone (2 mg/kg PO q24h) was administered to 27 German shepherds with canine anal furunculosis for 2 weeks, followed by a reduced dose (1 mg/kg PO q24h) for an additional 4 weeks. Maintenance prednisolone therapy (1 mg/kg PO q48h) was then administered for varying durations (8 to 16 weeks). All 27 dogs completed the study, with 33.3% of them showing complete resolution.

One-third of the dogs improved with therapy, and one-third remained unchanged as far as lesional score. In most of the corticosteroid-treated dogs, associated clinical signs (tenesmus, hematochezia, frequent defecation) were reduced regardless of the extent of perianal lesion improvement at the end of the study. The resolution of associated clinical signs alone was a satisfactory outcome to owners for most cases in which lesions did not resolve. It is noteworthy that in addition to corticosteroids, all dogs received an altered protein diet during this study (Harkin et al 1996)

- We have used **glucocorticoids** with reasonable success but usually combined with either **azathioprine** or **metronidazole**. This therapy is not cost prohibitive for most clients.
- **Prednisolone** should be initiated at immunosuppressive dose (2 to 4 mg/kg PO q24h or divided q12h), usually for 3 to 6 weeks to reduce pain, inflammation, and the extent of sinus tract involvement. Once the therapeutic goal has been achieved, the glucocorticoid dose should be slowly tapered over weeks to months to the lowest effective oral, every-other-day dose (ideally prednisone ≤ 1 mg/kg).
- **Azathioprine** suppresses both humoral and cell-mediated immunity and the potential side effects include gastrointestinal (GI) upset, bone marrow suppression, hepatotoxicity, and pancreatitis. When used as an adjuvant to glucocorticoids, azathioprine can be administered at 1.5 to 2.0 mg/kg/day PO for the first 2 to 4 weeks and then every other day.
- **Metronidazole** has immunomodulating effects, is effective at reducing faecal bacterial colonization of the perianal area, and is an antiprotozoal. Its potential side effects include anorexia, GI upset, central nervous system toxicity, and hepatotoxicity. We occasionally administer metronidazole (10 to 15 mg/kg PO q12h) in combination with glucocorticoids.

Management of perianal fistulae in five dogs using azathioprine and metronidazole prior to surgery. Aust Vet Journal 77(6): 374-378

A study was conducted to ascertain the effectiveness of combination azathioprine and metronidazole therapy prescribed once daily for 6 weeks before surgery (excision of sinus tracts and anal sacculotomy). Time to maximal improvement before surgery ranged from 3 to 6 weeks. During the first 2 weeks, associated clinical signs (anal irritation, licking, dyschezia, tenesmus) resolved in all five German shepherds. Although the perianal fistulas did not completely resolve, all lesions became smaller with less inflammation. After surgery, all lesions resolved with no recurrences (follow-up period: 7 to 10 months). Post surgical medical treatment was continued for 2 to 6 weeks. Of importance, the investigators found that medical therapy before surgery greatly facilitated surgical success. (Tisdall 1999). We do not have experience with this combination of medical and surgical therapy; however, we share the belief that surgical therapy is more effective after medical therapy

CYCLOSPORIN (CSA)

- CsA appears to be the **most effective medical treatment** to date for canine anal furunculosis. Table 1 summarizes the results of all the published trials utilising either CsA alone or in combination with ketoconazole.
- The **most effective therapeutic dosing regimen has not yet been clearly established**. In most studies, CsA was given twice daily but data from recent studies suggest that once daily administration is as beneficial as twice daily dosing.
- Lesion resolution appears to be more rapid with the higher dosages, but clinical signs also improved with dosages ranging from as low as 2 to 5 mg kg⁻¹. Short protocols with high dosages resulted in fast remission and high recovery rates, but they were likely to be followed by relapses of clinical signs after the discontinuation of treatment. Longer treatment protocols (> 13 weeks) decrease the rate of relapse.

GIVING KETOCONAZOLE WITH CYCLOSPORIN

- Coadministration of ketoconazole with CsA has been advocated to reduce the daily CsA dose and hence cost to clients. Ketoconazole inhibits CsA-metabolizing enzymes (i.e., cytochrome P-450 system), thereby decreasing CsA clearance while increasing CsA blood concentration.
- The level of metabolizing enzyme inhibition is quite variable among individuals. Therefore, the resulting CsA blood concentration is variable and cannot be predicted. It should also be remembered that ketoconazole has its own adverse side effects and drug interactions that might prohibit its use.

- The co-administration of ketoconazole decreases the dose of CsA needed to induce remission. A dosage of **1 mg kg⁻¹ of CsA combined with 10 mg kg⁻¹ of ketoconazole for 16 weeks** was found to be effective in one study (Mouatt et al 2002) and is currently the protocol we use in the dermatology clinic.
- Other clinicians prefer to use a **higher induction dose of 5 mg kg⁻¹ CsA in combination with 5 mg kg⁻¹ of ketoconazole** for a shorter induction period of **6 to 12 weeks** before tapering the CsA dose (beginning with a reduced daily dose is typical). If adverse effects are noted during ketoconazole administration, CsA trough blood levels should be determined by high-pressure liquid chromatography to rule out potential CsA cytotoxicosis. Also, ketoconazole administration should be discontinued and the cyclosporin dose either reduced or discontinued pending CsA blood level results.
- Once clinical signs have substantially resolved, either the dose of CsA can be reduced by 20% to 40% and given daily or the same dose can be administered every other day. Continued dose tapering should be based on clinical response and lack of relapse. Tapering CsA too quickly is a frequent cause of clinical relapse.

MEASURING CYCLOSPORIN TROUGH LEVELS

- A direct relationship between CsA blood trough concentration and clinical efficacy in treating canine anal furunculosis has not been definitively proven and we do not routinely measure CsA trough blood levels. This tool should be reserved for select patients, such as those receiving concurrent ketoconazole, those not improving as expected, and those in which drug toxicosis is suspected. When trough levels are needed, the high-pressure liquid chromatography method is recommended. Unfortunately, this method is available in only select laboratories and is expensive.

Table 1. Results of CsA Therapy for Canine Anal Furunculosis

Reference	Year Published	Oral Dosing	Pertinent Findings
Mathews et al	1997	CsA (7.5–10 mg/kg q12h for 20wk) 80% of dogs required either trimethoprim–sulfamethoxazole (15 mg/kg q12h) or cephalexin (25 mg/kg q12h) for varying durations.	100% of dogs showed progressive improvement in associated signs and lesions after 1 wk. Total resolution occurred in 100% of dogs after 20 wk. Remission lasted 6–18 mo or more after treatment ended.
Mathews et al	1997	CsA (5 mg/kg q12h for 16 wk) 100% of dogs were treated with cephalexin (20 mg/kg q12h for 10 days).	The study was randomized, blinded, and placebo-controlled during the initial 4 wk. 100% of dogs improved with CsA therapy; 0% improved when administered a placebo. Several associated signs significantly improved within 4 wks. After 16 wk, 85% of dogs completely healed and the remaining dogs showed improvement. The disease recurred in 41% of dogs after treatment ended. The authors acknowledged that CsA blood concentration and efficacy may not be related.
Griffiths et al,	1999	CsA (7.5 mg/kg q12h for 10–20 wk) No concomitant antibiotherapy was administered.	The average lesion reduction was 75% in all dogs within 1 wk. 100% of associated signs improved within 1 wk Lesions continued to resolve over 10–20 wk. The recurrence rate was 17% during follow-up (mean: 7.7 mo). There was poor correlation between CsA blood concentration and efficacy (at least after the first week).
Hardie et al ¹⁶	2000	CsA (4 mg/kg q12h until resolution [mean: 8.8 wk]) There was no mention of concurrent antibiotherapy.	96% of dogs showed improvement; complete remission in 72% The recurrence rate was 36% during follow-up (mean: 6.8 mo). Lesion recurrence averaged 10.6 wk after treatment ended.

Table 1. Results of Cyclosporine A (CsA) Therapy (continued)

Reference	Year Published	Oral Dosing	Pertinent Findings
Mouatt ⁹ , Et al a	2002	<p>CsA did not exceed 1 mg/kg q12h for 16 wk</p> <p>Ketoconazole (10 mg/kg q24h for 16 wk)</p> <p>Antibiotherapy was given for concurrent conditions</p>	<p>100% of dogs showed >50% reduction in surface area and depth within 2 wk</p> <p>100% of associated signs improved within 2 wk</p> <p>Complete resolution occurred in 93% of dogs</p> <p>50% of dogs that had complete resolution were disease free for >1 yr.</p> <p>To maintain CsA at therapeutic blood levels, the dose of CsA was reduced 80%–90% when administered with ketoconazole. There was no consistent relationship between CsA blood concentration and efficacy.</p>
Patricelli Et al a	2002	<p>CsA (2.5 mg/kg q12h or 4 mg/kg q24h [duration not specified])</p> <p>Ketoconazole (~8 mg/kg q24h in all dogs)</p> <p>There was no mention of concurrent antibiotherapy.</p>	<p>Resolution of associated clinical signs occurred within 9 wk in all dogs.</p> <p>Significant lesion improvement occurred in all dogs (mean time to remission: 14 wk).</p> <p>63% of dogs that experienced remission had a mean time to recurrence of 12.4 wk.</p> <p>All dogs that experienced recurrence had moderate to severe disease at the initial examination.</p>
Doust Et al a	2003	<p>CsA (1.5, 3, 5, or 7.5 mg/kg q24h for 13 wk)</p> <p>If clinical signs continued after 13 wk, owners could continue administering CsA.</p> <p>There was no mention of concurrent antibiotherapy.</p>	<p>Lesions and associated signs improved faster with the highest dose. The rate of complete resolution was highest in dogs administered the highest dose.</p> <p>A longer (> 12 mo) remission Or controlled response occurred regardless of the dose when dogs were treated for > 13 wk</p> <p>There was no consistent relationship between CsA blood concentration and efficacy.</p>

Table 1. Results of Cyclosporine A (CsA) Therapy (continued)

Reference	Year Published	Oral Dosing	Pertinent Findings
O'Neill Et al ^a	2004	CsA (0.5, 0.75, 1, or 2 mg/kg q12h [duration not specified; 3–10 wk?]) Ketoconazole (5–9 mg/kg q24h) Amoxicillin–clavulanic acid (12.5 mg/kg) or cephalexin (15 mg/kg q12h) was administered for 7 days before CsA and ketoconazole.	Resolution of clinical signs began in 1 to 2 weeks Lesions resolved in all dogs by 10 wk, but dramatic improvement occurred in the initial 2 wks. There was no correlation between the severity of lesions and duration of treatment. 63% of dogs remained in remission for 1–19 mo. Most dogs had CsA levels that exceeded therapeutic blood levels regardless of the dose of CsA. Significant interindividual variation occurred in CsA blood levels with similar drug doses. There was a cost reduction of 70% compared with using CsA (5 mg/kg q12h) alone.

^a The microemulsified form of cyclosporine was prescribed. The target CsA blood trough concentration was usually 400–600 ng/ml. The associated signs (e.g., tenesmus, constipation, increased frequency of defecation, perianal licking, self-mutilation) varied with each study. Adjunctive surgical therapy was needed in several studies.

Table from Patterson AP and Campbell KL Managing Anal Furunculosis in Dogs Compendium of Continuing Education May 2005, p 348 to 349

Immunosuppressive or Immunomodulatory Therapy: Maintenance

TACROLIMUS

- Tacrolimus has pharmacologic actions very similar to those of CsA but is 10 to 100 times more potent. It is applied topically to dogs because systemic administration requires careful drug monitoring. All studies thus far indicate that significant levels of tacrolimus do not accumulate in the blood when it is given topically. The drug is currently used as a topical immunomodulator in children and adults with atopic eczema. The most common side effects in humans are stinging and burning.
- Topical tacrolimus (Protopic 0.1% ointment, Fujisawa Health Care) has been reported to completely heal sinus tracts in 50% of dogs or markedly improve lesions in 90% of dogs when applied once or twice daily to treat anal furunculosis. In this study, the severity of canine anal furunculosis was graded as mild to moderate before therapy. In dogs that healed completely with several months of remission, tacrolimus was applied up to 16 weeks. No major complications were reported in any of the dogs (Misseghers 2000).
- If clinical signs of canine anal furunculosis are relatively mild at initial presentation and the dog does not object to topical therapy, tacrolimus may be administered alone. Tacrolimus is not approved for use in dogs.
- As induction therapy is tapered, topical tacrolimus can be applied to the perianal region twice daily using a gloved hand. Induction therapy tends to be greatly reduced with concurrent tacrolimus therapy. We continue topical tacrolimus indefinitely regardless of whether induction therapy can be completely discontinued. Application of tacrolimus should be reduced to the lowest frequency that controls inflammation (usually every 24 to 72 hours). If tacrolimus is not used, the lowest possible dose of induction therapy should be given every 24 to 72 hours, depending on the drug(s) used.

Hygiene Therapy

- Antibiotic therapy is recommended to control secondary infection and antibiotic selection should be based on bacterial culture and susceptibility results. Empiric therapy with either amoxicillin–clavulanic acid or metronidazole is useful, pending culture results. Once the patient tolerates topical therapy, mupirocin ointment (Bactroban, Pfizer) applied once or twice daily may help reduce bacterial colonization.
- It is important to keep the perianal region clean and dry. Clipping and cleaning the perianal region under sedation can assist. Baby powder lightly applied to the surrounding perineum may reduce regional relative humidity. At home, antimicrobial shampoo therapy may be helpful once the patient will tolerate it.

MONITORING

- Reexaminations are usually scheduled every 6 weeks. Tracking the degree of improvement in clinical signs since the initial visit is important at each reexamination.
- Signs include tenesmus, dyschezia, hematochezia, constipation or obstipation, diarrhoea, ribbon-like stool, increased frequency of defecation, perianal licking, self-mutilation, perianal pain, scooting, offensive odour, low tail carriage, and weight loss. Although there may be several small sinus tracts, the owner may be satisfactorily impressed if signs of pain are reduced. Cutaneous reepithelialization may occasionally supersede the filling of sinus tracts, resulting in epithelialized tunnels, which were not associated with clinical problems in one study (Mouatt 2002)
- One of the most useful tools for monitoring improvement in canine anal furunculosis is a rectal examination while the patient is not sedated. Patients become less hesitant and require less restraint during rectal examinations as their clinical signs, specifically pain, improve. However, sedation is often needed during the first few reexaminations. The perianal, anal, and rectal tissues should be assessed. The anal sacs should be palpated and expressed if needed. The degree of tissue thickening (i.e., fibrosis) should be assessed during the rectal examination. In general, tissue thickening gradually reduces with time in patients that respond to treatment. Perianal cytology can be used to determine whether antibacterial treatments are still indicated.

ADJUNCTIVE TREATMENT

- Unfortunately, all dogs with anal furunculosis do not completely respond to medical management alone. Adjunctive surgical therapy is warranted if affected tissue hinders improvement in pain and/or healing or inflammation continues to expand despite aggressive medical treatment. Despite differences among surgical techniques previously described, the goal of surgical treatment is to remove or destroy diseased tissue. This may include anal sacculotomy. As previously noted, it appears that surgical outcomes improve with prior medical treatment.
- The carbon dioxide laser has been an effective adjunctive tool in treating canine anal furunculosis in some dermatology practices in the US. Lasers are used to ablate and/or excise ulcerative necrotic tissue in patients with canine anal furunculosis.

FUTURE TREATMENTS

- To achieve and maintain remission in humans with Crohn's disease, several new and emerging therapeutic options are being used. Many of these agents are designed to precisely block or enhance immunologic events (i.e., cell signalling, leukocyte adhesion) believed to be involved in the pathogenesis of Crohn's disease. Specifically, monoclonal anti-TNF- α antibodies (i.e., infliximab, certolizumab, adalimumab), soluble TNF- α receptor antagonists (i.e., etanercept), recombinant IL-10 (i.e., antiinflammatory cytokine), and intercellular adhesion molecule antagonists (i.e., natalizumab, alicaforsen) have been used with varying success in patients with Crohn's disease.
- In addition to these treatments, use of probiotics (i.e., products containing microorganisms that beneficially alter the compartmental microflora of a host; e.g., *Lactobacillus* spp) in patients with Crohn's disease is showing encouraging results.
- Perhaps once the veterinary community elucidates the immunopathogenesis of canine anal furunculosis, similar specific immune-altering therapies may prove useful in managing the disease.

REFERENCES

- Matushek KJ, Ederhard R: Perianal fistulas in dogs. *Compend Contin Educ Pract Vet* 13(4):621–627, 1991.
- Day MJ, Weaver BM: Pathology of surgically resected tissue from 305 cases of anal furunculosis in the dog. *J Small Anim Pract* 33:583–589, 1992.
- Mathews KA, Ayres SA, Tano CA, et al: Cyclosporin treatment of perianal fistulas in dogs. *Can Vet J* 38:39–41, 1997.
- Mathews KA, Sukhiani HR: Randomized controlled trial of cyclosporine for the treatment of perianal fistulas in dogs. *JAVMA* 211(10):1249–1253, 1997.
- Killingsworth CR, Walshaw R, Dunstan RW, et al: Bacterial population and histologic changes in dogs with perianal fistula. *Am J Vet Res* 49(10):1736–1741, 1988.
- Doust R, Griffiths LG, Sullivan M: Evaluation of once-daily treatment with cyclosporine for anal furunculosis in dogs. *Vet Rec* 152(8):225–229, 2003.
- Ellison GW: Treatment of perianal fistulas in dogs. *JAVMA* 206(11):1680–1682, 1995.
- Griffiths LG, Sullivan M, Borland WW: Cyclosporin as the sole treatment for anal furunculosis: Preliminary results. *J Small Anim Pract* 40:569–572, 1999.
- Mouatt JG: Cyclosporin and ketoconazole interaction for the treatment of perianal fistulas in the dog. *Aust Vet J* 80(4):207–211, 2002.
- Patricelli AJ, Hardie RJ, McAnulty JF: Cyclosporine and ketoconazole for the treatment of perianal fistulas in dogs. *JAVMA* 220(7):1009–1016, 2002.
- Harkin KR, Walshaw R, Mullaney TP: Association of perianal fistula and colitis in the German shepherd dog: Response to high-dose prednisone and dietary therapy. *JAAHA* 32:515–520, 1996.
- Tisdall PLC, Hunt GB, Beck JA, et al: Management of perianal fistulae in five dogs using azathioprine and metronidazole prior to surgery. *Aust Vet J* 77(6):374–378, 1999.
- Misseghers BS, Binnington AG, Mathews KA: Clinical observations of the treatment of canine perianal fistulas with topical tacrolimus in 10 dogs. *Can Vet J* 41:623–627, 2000.
- O'Neill T, Edwards GA, Holloway S: Efficacy of combined cyclosporine A and ketoconazole treatment of anal furunculosis. *J Small Anim Pract* 45:238–243, 2004.
- Hardie RJ, Gregory SP, Tomlin J, et al: Cyclosporine treatment of perianal fistulae in 26 dogs. *Vet Surg* 29(5):481, 2000.
- Brookes MJ, Green JR: Maintenance of remission in Crohn's disease: Current and emerging therapeutic options. *Drugs* 64(10):1069–1089, 2004.
- MacPherson A, Khoo UY, Forgacs I, et al: Mucosal antibodies in inflammatory bowel disease are directed against intestinal bacteria. *Gut* 38:365–375, 1996.
- Day MJ: Immunopathology of anal furunculosis in the dog. *J Small Anim Pract* 34:381–389, 1993.

- Vasseur PB: Results of surgical excision of perianal fistulas in dogs. *JAVMA*185(1):60–62, 1984.
- Houlton JE: Anal furunculosis: A review of seventy cases. *J Small Anim Pract* 21:575–584, 1980.
- Budsberg SC, Robinette JD, Farrell RK: Cryotherapy performed on perianal fistulas in dogs (Washington State University 1976–1980). *Vet Med Small Anim Clin* 667–669, 1981.
- Goring RL, Bright RM, Stancil ML: Perianal fistulas in the dog: Retrospective evaluation of surgical treatment by deroofting and fulguration. *Vet Surg*15(5):392–398, 1986.
- Elkins AD, Hobson HP: Management of perianal fistulae: A retrospective study of 23 cases. *Vet Surg* 11:110–114, 1982.
- Ellison GW, Bellah JR, Stubbs WP, et al: Treatment of perianal fistulas with ND:YAG laser: Results in twenty cases. *Vet Surg* 24:140–147, 1995.
- Van Ee RT, Palminteri A: Tail amputation for the treatment of perianal fistulas in dogs. *JAAHA* 23:95–100, 1987.
- Sandborn WJ, Tremaine WJ, Lawson GM: Clinical response does not correlate with intestinal or blood cyclosporine concentrations in patients with Crohn's disease treated with high-dose oral cyclosporine. *Am J Gastroenterol* 91(1):37–43, 1996.
- Present DH, Lichtiger S: Efficacy of cyclosporine in treatment of fistula of Crohn's disease. *Dig Dis Sci* 39:374–380, 1994.
- Cat H, Sophani I, Lemann M, et al: Cyclosporin treatment of anal and perianal lesions associated with Crohn's disease. *Turk J Gastroenterol* 14(2):121–127, 2003.
- Guaguere E, Steffan J, Olivry T: Cyclosporin A: A new drug in the field of canine dermatology. *Vet Dermatol* 15:61–74, 2004.
- Dahlinger J, Gregory C, Bea J: Effect of ketoconazole on cyclosporine dose in healthy dogs. *Vet Surg* 27:64–68, 1998.
- Nghiem P, Pearson G, Langley RG: Tacrolimus and pimecrolimus: From clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *J Am Acad Dermatol* 46(2):228–241, 2002.
- Wiederrecht G, Lam E, Hung S, et al: The mechanism of action of FK-506 and cyclosporin A. *Ann N Y Acad Sci* 696:9–19, 1993.
- Hnilica KA: How useful is topical tacrolimus in treating perianal fistulas? *VetMed* 324–326, 2004.
- Shelley BA: Use of the carbon dioxide laser for perianal and rectal surgery, in Bartels KE (ed): *Vet Clin North Am Small Anim Pract (Lasers in medicine and surgery)*. 32(3):621–637, 2002.