Article #1

Managing Anal Furunculosis in Dogs

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ABSTRACT:

Canine anal furunculosis (perianal fistula) is a chronic disease of the perianal, anal, and/or rectal tissue characterized by the presence of ulcerative tracts. The specific cause of this debilitating disease is unknown and continues to be controversial. Nevertheless, a multifactorial immune-mediated mechanism is suspected. Diagnosis is usually straightforward in German shepherds presenting with perianal lesions and associated clinical signs. Although canine anal furunculosis was once considered a primary surgical disease, medical management is now the initial treatment of choice. Management includes immunosuppressive, hygiene, and dietary therapy. It is critical to inform clients of the relapsing and remitting course of this inflammatory disease.

Canine anal furunculosis (perianal fistula) is a chronic, painful, progressive inflammatory and ulcerative disease associated with the perianal, anal, and/or perirectal tissues.[1] The disease is characterized by the presence of focal or multifocal dissecting ulcerative tracts, usually with concurrent malodorous mucopurulent discharge (Figures 1 and 2). Canine anal furunculosis has a clinical appearance similar to that of perianal fistula in humans, which is often associated with granulomatous enteritis (i.e., Crohn's disease).[2–4] Although true rectocutaneous and anocutaneous fistulas can occur, they appear to be rare in canine anal furunculosis.[1,3] More commonly, epithelial-lined sinus tracts develop in the perianal tissue. These ulcerative tracts of varying diameter, depth, and connectivity can extend 360° circumferentially around the anus. German shepherds with this disease appear to be overrepresented, with one report showing that 84% of affected dogs were German shepherds.[2] Other breeds reported to have canine anal furunculosis include Irish setters, collies, Border collies, Old English sheepdogs, Labrador retrievers, English bulldogs, beagles, Bouvier des Flandres, spaniels, and mixed breeds.[1–3,5–7] The disease usually affects middle-aged dogs; the mean age is reportedly 4 to 7 years.[2] A sex predilection has not been definitively described. Clinical signs prompting veterinary care are listed in the box on page 342.[1,3,4,6–14] The anatomy of the anal region is described in the other box on page 342.[15] Considering the lack of success with previous therapies, many owners have low expectations in treating canine anal furunculosis.

PATHOGENESIS

A definitive cause of anal furunculosis has not been described; however, many theories have been proposed. The more common hypotheses have included poor conformation of the perianal region and tail (i.e., broad-based low tail carriage), anal crypt fecalith impaction resulting in abscessation, spread of infection from the anal glands or anal sacs, trauma, and foreign body reaction. Unfortunately, little evidence supports

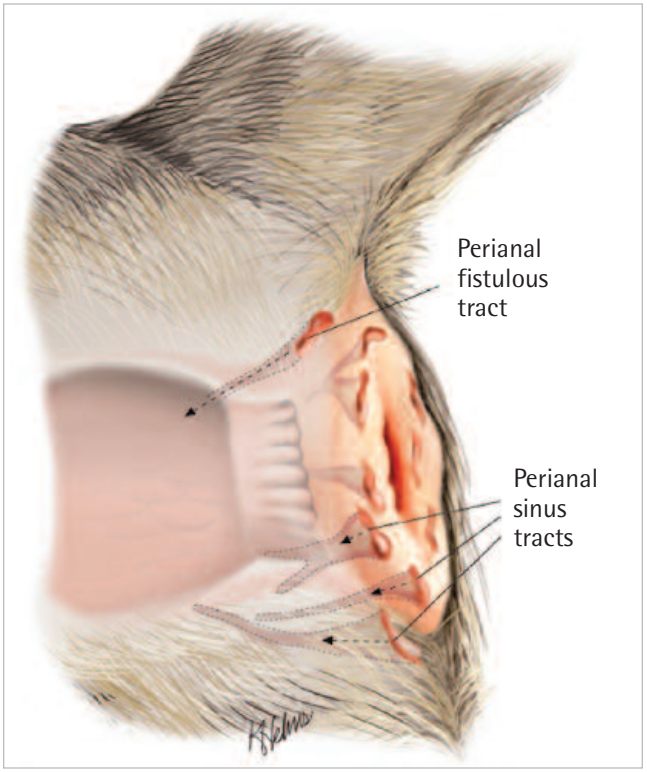


Figure 1. Circumferential perianal sinus tracts and fistula in a dog. (Illustration by Mr. Kerry Helms)

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 down-regulating the immune response.[3,4,6,8,10–13,16,17] Accumulating evidence shows that Crohn's disease is the result of an unbalanced host immune response to intestinal triggers in genetically susceptible humans.[17–19] Because German shepherds with canine anal furunculosis also have clinical and histologic evidence of colitis (i.e., inflammatory bowel disease [IBD]), perhaps enteral triggers (i.e., dietary antigens, bacterial antigens, superantigens) are initiators of canine anal furunculosis as well.[11] This is an interesting speculation because the German shepherd, the breed most often reported to have canine anal furunculosis, also commonly has IBD.[20] Maybe the genetic makeup of some German shepherds produces heightened proinflammatory immune responses, resulting in immune-mediated diseases. However, one study was unable to identify at least a simple immunologic defect as an underlying factor in the predisposition of German shepherds to canine anal furunculosis.[21] Another proposed initiating factor of canine anal furunculosis is staphylococcal folliculitis.[21]

Based on histologic evaluation, early canine anal furunculosis lesions show an inflammatory reaction associated with epidermal appendages without concomitant epidermal ulceration.[5] As the inflammatory reaction intensifies, folliculitis/furunculosis and nonarborizing sinus tracts develop in the perianal dermis. Perifollicular, superficial epidermal ulceration and arborizing dissecting cellulitis soon follow throughout the perianal tissue.[5] The sinus tracts are typically lined by squamous epithelium and are infiltrated with a mixture of lymphocytes, plasma cells, macrophages, neutrophils, and eosinophils. As perianal lesions progress, peripheral lymphoid nodules (predominantly T lymphocytes) develop, along with extensive granulating fibrosis.[2,5,21] Interestingly, it appears that anal sac disease usually occurs as a result of expanding inflammation.[1,2]

PHYSICAL EXAMINATION

Examination of the perianal area of patients with anal furunculosis typically requires sedation or general anesthesia because of severe pain. Clipping the perianal

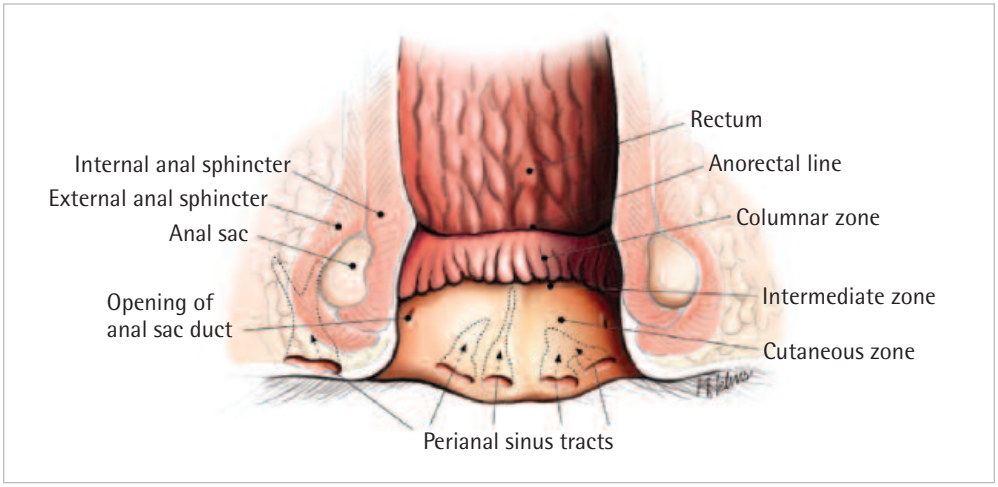


Figure 2. Rectum and anal canal anatomy (opened along the middorsal line) depicting sinus tract lesions. (Illustration by Mr. Kerry Helms)

Clinical Signs of Canine Anal Furunculosis[1,3,4,6–14]

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

Anatomy of the Anal Region

Anal canal—Small portion of the alimentary canal that extends from the terminal part of the rectum to the anus. It is roughly 1 cm long. The internal anal sphincter (involuntary smooth muscle) and the external anal sphincter (voluntary striated muscle) are positioned between the rectum and anus. Sensory and motor functions are supplied by the pudendal nerve and its branches.[15]

Anal sacs—Spherical reservoir sacs that are invaginations between the internal and external anal sphincter muscles. One sac is on each side of the anal canal. Their ducts open onto the cutaneous zone. The sac walls contain coiled apocrine sweat glands with scattered sebaceous glands.[15]

Anus—Terminal opening of the alimentary canal. The anal tissue is divided (from cranial to caudal) into the columnar, intermediate, and cutaneous zones.[15]

Columnar zone—Contains longitudinal ridges (i.e., anal columns) with shallow valleys (i.e., anal sinuses) that terminate caudally as blind pockets (i.e., anal crypts) at the anocutaneous line (i.e., intermediate zone), resulting in a scalloped fold. It contains modified tubuloalveolar sweat glands.

Cutaneous zone—Contains an inner hairless portion and an outer relatively hairless portion that are part of the mucocutaneous junction. The anal sac ducts open onto the inner portion of this zone at the lateral angles of the anus. This zone contains circumanal (hepatoid), sebaceous, and apocrine sweat glands.

Intermediate zone—Also known as the *anocutaneous line*, it spans the perimeter of the anal canal. It is less than 1 mm wide. This zone also contains modified tubuloalveolar sweat glands.

Rectum—Caudal portion of the large intestines that lies within the pelvic canal. The boundary between the rectum and anal canal is known as the *anorectal line*, which is marked by transition from columnar to stratified squamous epithelium[15] (Figure 2).

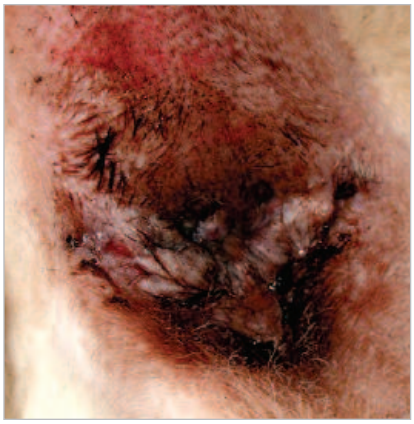
region might be necessary to fully assess the severity of disease. Lesions may vary from superficial pinpoint tracts to large ulcerated areas (Figure 3). Several of these tracts may often be interconnected. Tracts may tunnel deep within the surrounding tissue and occasionally communicate with the rectum, anus, and/or anal sacs. The tracts should be probed with a sterile, blunt instrument to determine their extent and involvement with regional structures. The external anal sphincter, anal sacs, and rectal mucosa should be assessed. 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 diagnostic differentials include anal sac abscessation, perianal adenoma, anal sac adenocarcinoma, anal squamous cell carcinoma, rectal neoplasia, atypical bacterial infection, mycosis, and oomycosis (i.e., pythiosis, lagenidiosis).

DIAGNOSTIC EVALUATION

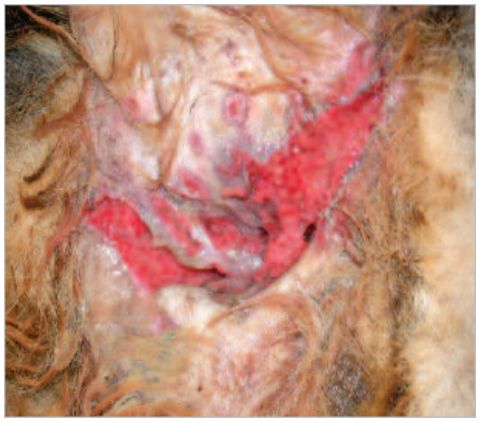
The diagnosis of canine anal furunculosis is based on history, physical examination findings, and ruling out other primary diagnostic differentials. Obtaining a minimum database is always at the discretion of the clinician, but a complete blood count, serum biochemical profile, and urinalysis are useful before anesthesia and to rule out concurrent diseases. 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 are usually allowed to heal by second intention. A restrictive diet trial should be implemented to rule out concurrent adverse food reactions. Other diagnostics that may prove helpful include fecal flotation cytology, rectal scraping cytology, fungal culture, colonoscopy with biopsy, and pelvic radiography.

Figure 3. Clinical presentation of canine anal furunculosis.



Perianal region of a German shepherd with a mild form of canine anal furunculosis. Note the weeping ulcerative tracts at 3 and 9 o'clock and the thickened ventral anus.



Severe form of canine anal furunculosis in a German shepherd. Note the extensive ulcerative and granulating area circumferentially around the anus, along with the scattered small sinus tracts.

MANAGEMENT

Primary surgical treatment of canine anal furunculosis was previously advocated. Surgical procedures focus on either destroying the epithelial lining of sinus tracts or total en bloc tract excision to remove diseased tissue and prevent recurrence. Surgical treatment has included surgical excision, chemical cauterization, cryotherapy, deroofing and fulguration, and laser (i.e., neodymium: yttrium aluminum garnet) excision.[1,7,22–27] Tail amputation has also been recommended as a means of reducing fecal soiling and contamination over the perianal area.[28] These procedures have reportedly had varying success rates (i.e., 48% to 97% of cases).[1,27] However, the recurrence rate has approached 70%, with some surgical techniques necessitating further surgical treatments.[1] Other frequent complications such as anal stenosis (in up to 15% of cases, with the incidence approaching 47% following cryotherapy) and fecal incontinence (in up to 29% of cases) should not be taken lightly because these factors likely contribute to an owner's ultimate decision of euthanasia.[1]

Fortunately, medical management in recent years has shed new light on this devastating disease. Cyclosporine A (CsA) has been effective in managing Crohn's disease in humans.[29–31] The clinical parallels between canine anal furunculosis and Crohn's disease have led veterinary investigators to hypothesize that medical management of Crohn's disease should be applicable to canine anal furunculosis. Indeed, several studies have reported favorable results with immunosuppressive or immunomodulating drug regimens, including CsA, tacrolimus, and azathioprine and metronidazole.[3,4,6,8–10,12–14] Conventional immunosuppression with glucocorticoids has also been reported, albeit without the same level of success.[11] Consequently, clinicians can now give their clients new therapeutic options that can positively affect the prognosis. Moreover, anal stenosis and fecal incontinence are rare complications with these medical treatments.

It is paramount for clinicians to discuss with clients the goal, effectiveness, length, and cost of therapy before implementing it. Likewise, 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. In our opinion, the first goal of therapy should be to alleviate large bowel clinical signs such as tenesmus, dyschezia, hematochezia, consti-

Canine anal furunculosis is a chronic relapsing and remitting inflammatory disease.

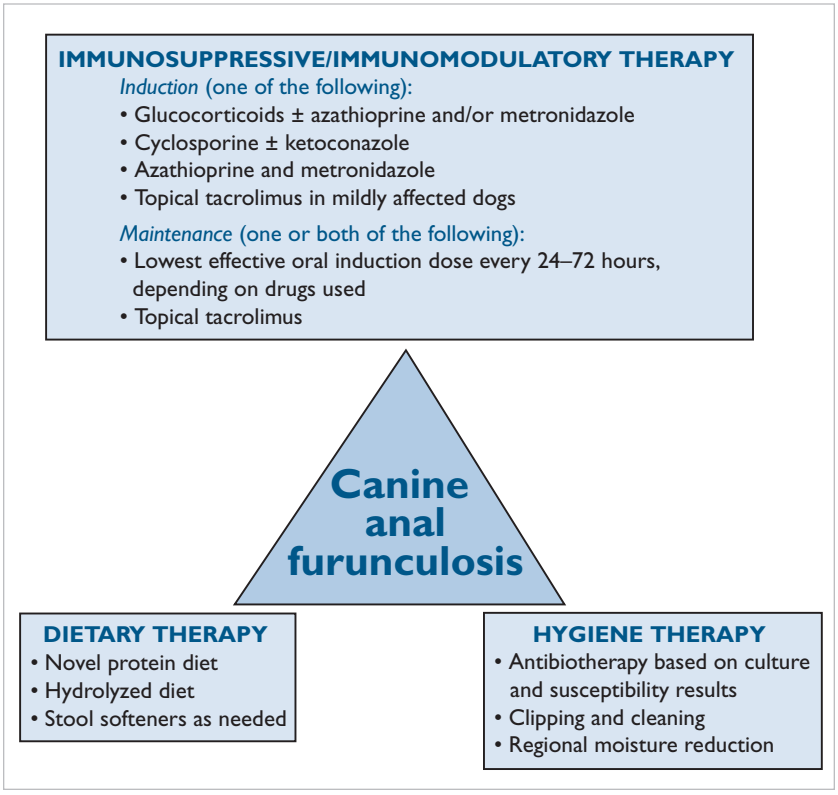


Figure 4. Medical triad approach to managing canine anal furunculosis.

pation 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, hygiene, and dietary therapy (Figure 4). 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

Every clinician should be aware of the benefits and risks associated with glucocorticoids and should outline them for clients. Specifically, glucocorticoids can quickly reduce inflammation by inhibiting eicosanoid synthesis (i.e., prostaglandins, thromboxanes, leukotrienes), inhibiting proinflammatory cytokine synthesis (i.e., interleukin [IL]-1 and 6, tumor necrosis factor [TNF]-α), decreasing leukocyte chemotaxis and adherence, decreasing antigen presentation capabilities, decreasing lymphocyte cytokine synthesis important in cell signaling (i.e., IL-2, 3, 4, and 5; interferon-γ), and causing many other antiinflammatory effects.[32] For the most part, glucocorticoids suppress cell-mediated immunity with very little effect on humoral immunity. Unwanted side effects (e.g., polydipsia, polyuria, polyphagia, susceptibility to infection, cutaneous atrophy, muscle wasting, panting, insulin antagonism) may preclude glucocorticoid administration in some animals.

Glucocorticoids have reportedly been used to treat canine anal furunculosis.[11] Prednisone (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 prednisone 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 (i.e., tenesmus, hematochezia, frequent defecation) were reduced regardless of the extent of perianal lesion improvement at the end of the study. The investigators mentioned that 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.[11]

We have used glucocorticoids with reasonable success but at higher doses and usually combined with either azathioprine or metronidazole, similar to treatment of other immune-mediated diseases.[20,33,34] This therapy is not cost prohibitive for most clients. Prednisone should be initiated at a high immunosuppressive dose (3 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 is metabolized to an active antimetabolite, which interferes with nucleic acid synthesis.[35] Azathioprine suppresses both humoral and cell-mediated immunity. Most veterinarians are familiar with potential azathioprine side effects, including gastrointestinal (GI) upset, bone marrow suppression, hepatotoxicity, and pancreatitis.[35] When used as an adjuvant to glucocorticoids, azathioprine can be administered at 1.5 to 2.2 mg/kg/day PO for the first 2 to 4 weeks and then every other day. We occasionally administer metronidazole (10 to 15 mg/kg PO q12h) in combination with glucocorticoids. Metronidazole has immunomodulating effects, is effective at reducing fecal bacterial colonization of the perianal area, and is an antiprotozoal.[20,34,36] Its potential side effects include anorexia, GI upset, central nervous system toxicity, and hepatotoxicity.[36]

A study was conducted to ascertain the effectiveness of combination azathioprine and metronidazole therapy before surgery (i.e., excision of sinus tracts and anal sacculectomy).[12] Both of these drugs were prescribed once daily for 7 to 28 weeks before surgery. Time to maximal improvement before surgery ranged from 3 to 6 weeks. During the first 2 weeks, associated clinical signs (i.e., anal irritation, licking, dyschezia, tenesmus) resolved in all five German shepherds. Although the perianal fistulas did not completely resolve before surgery, all lesions became smaller and/or shallower with less inflammation. After surgery, all lesions resolved with no recurrences (follow-up period: 7 to 10 months). Postsurgical medical treatment was continued for 2 to 6 weeks. Of importance, the investigators found that medical therapy before surgery greatly facilitated surgical success. 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.

CsA can be isolated from extracts of telluric fungi (i.e., *Tolypocladium inflatum gams*).[37] This immunomodulating drug gained popularity in the late 1970s as a treatment to prevent organ transplant rejection in humans. In addition, CsA has been effective in treating several human dermatoses.[37,38] CsA has recently been shown to be effective in treating canine atopic dermatitis and canine anal furunculosis.[3,4,6,8–10,14,16,39,40] Over the past several years, data have been collected on the pharmacokinetics and safety of this drug in dogs.

CsA, a reversible immunosuppressant/immunomodulator with low cytotoxicity, becomes active when bound to the intracellular receptor cyclophilin, an immunophilin (Figure 5). This complex inhibits cytosolic calcineurin, thereby blocking three calcium-dependent pathways: exocytosis, apoptosis, and enzymatic actions of calcineurin, such as IL-2 transcription.[37,41] Inhibition of IL-2 synthesis leads to impaired T-lymphocyte activation or proliferation and further cytokine synthesis, thus down-regulating immune amplification signals. CsA does not appear to alter humoral immunity.[41] The drug might have other mechanisms that affect keratinocyte kinetics.

Canine anal furunculosis can be managed but not necessarily cured. Medical management offers the best chance for resolution.

The first oral CsA formulation (Sandimmune, Sandoz) had a vegetable-oil base. There was much interindividual variability with this formulation because of its poor absorption. A microemulsion of CsA that is more bioavailable is now available, thus decreasing interindividual variability.[37,41] Atopica (Novartis) is the microemulsion form of CsA approved for controlling atopic dermatitis in dogs. The human equivalent to canine-approved CsA is Neoral (Novartis). Because of greater bioavailability and less interindividual variability, the microemulsion form of CsA is preferred. Because CsA absorption is slightly delayed when the drug is given with food, the recommendations are to administer it 2 hours before or after feeding.[41]

As with all drugs, clinicians should familiarize themselves with a given drug's pharmacokinetics, pharmacology, safety, adverse effects, and known drug interactions. The following summary is not intended to be completely comprehensive. It would behoove clinicians to read CsA

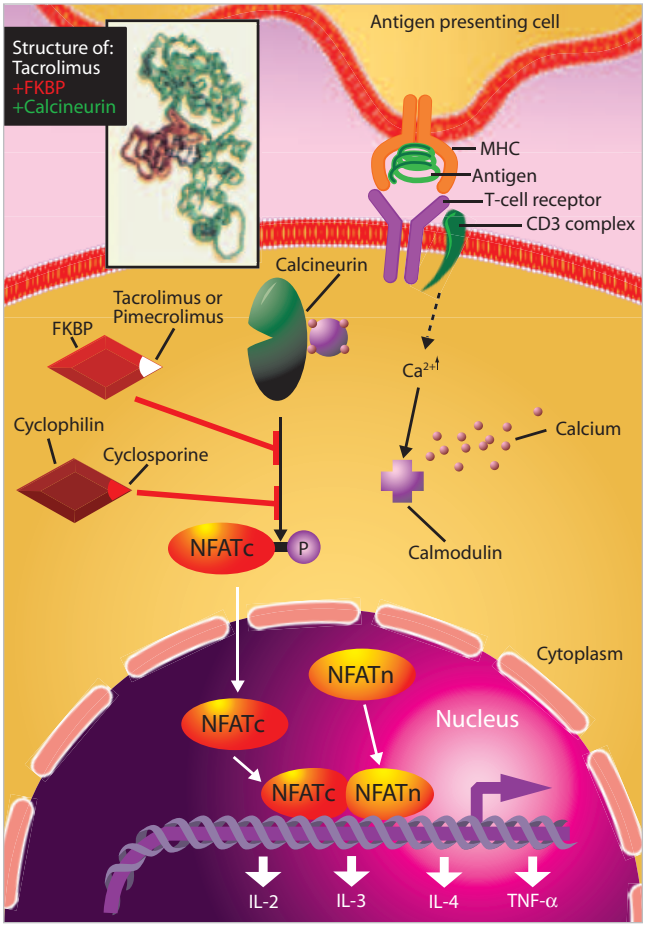


Figure 5. Molecular mechanism of inhibition of the immune response by tacrolimus, pimecrolimus, and cyclosporine. T-lymphocyte activation is initiated by interaction of antigenic peptide presented in the major histocompatibility complex to the appropriate T-cell receptor. Activation signals from the CD3 complex increase intracellular calcium and induce synthesis of the nuclear subunit of the nuclear factor of activated T cells (NFATn). Elevated free calcium in the cell binds to calmodulin, which binds and activates calcineurin, a critical calcium-activated protein phosphatase. Calcineurin causes dephosphorylation of the cytoplasmic subunit of NFAT (NFATc), allowing it to translocate to the nucleus. The newly synthesized nuclear subunit (i.e., NFATn) then binds to NFATc, and this essential complex facilitates transcription of numerous cytokines, including TNF-α and IL-2, 3, and 4. Tacrolimus, pimecrolimus, and cyclosporine block this normal activation pathway by inhibiting calcineurin function. First, the drug binds its intracellular ligand: Tacrolimus or pimecrolimus binds FK506-binding protein (FKBP) and cyclosporine binds cyclophilin. In each case, these complexes gain the ability to bind calcineurin and block its ability to dephosphorylate NFATc. In other cell types, such as mast cells, degranulation is a calcium-dependent event and is also blocked by tacrolimus or cyclosporine. *Inset:* The crystal structure of the complex of FKBP (in red), tacrolimus (in white), and calcineurin (in green) is modified from the x-ray crystal structure solved in 1995. The groove bound by FKBP-tacrolimus is adjacent to the active site on calcineurin and blocks the ability of substrate to interact with calcineurin effectively. (Reproduced with permission from Nghiem P, Pearson G, Langley RG: Tacrolimus and pimecrolimus: From clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *J Am Acad Dermatol* 46:228–241, 2002; the American Academy of Dermatology)

package inserts before administering the drug. In addition, there is an excellent review by Guaguere et al.[41]

CsA is metabolized by intestinal and liver cytochrome P-450 enzymes into what are believed to be inactive metabolites. Elimination is mainly biliary. The drug does not appear to be either nephrotoxic or hepatotoxic in dogs given extraordinarily high doses not routinely used in clinical practice. The more common adverse effects at routine doses include vomiting, diarrhea, gingival hyperplasia, papilloma-like skin lesions, hypertrichosis, and increased hair shedding.[41] These signs usually resolve with dose reduction or drug discontinuation. If GI upset occurs, we give the CsA with a small amount of food, the daily dose divided twice daily, or an antiemetic for several days until the patient tolerates it. To date, there are no data documenting an increased incidence of infections with CsA given at routine doses for canine atopic dermatitis and canine anal furunculosis. CsA should not be given to patients with neoplasia.

It is preferred to administer CsA once daily for canine atopic dermatitis because of the long half-life (about 9 hours) of CsA in dogs.[38,41] Although most canine anal furunculosis studies administered CsA twice daily, once-daily dosing is also effective in treating canine anal furunculosis.[6] Some investigators recommend obtaining CsA blood trough levels and adjusting the dose to increase the drug's effectiveness. However, target trough levels (400 to 600 ng/ml) are based on the CsA concentration needed to prevent allograft rejection.[38,41] Moreover, proposed target trough levels are based on twice-daily dosing used in humans, not the once-daily dosing usually recommended for dogs. A direct relationship between CsA blood trough concentration and clinical efficacy in treating canine anal furunculosis has not been definitively proven (Table 1). In fact, in humans with Crohn's disease treated with CsA (Sandimmune, Sandoz; 8 mg/kg/day PO in two divided doses), there was no correlation between clinical response and whole blood or intestinal CsA concentrations.[29] However, the formulation of CsA used in this report might have con-

Table 1. Results of Cyclosporine A (CsA) Therapy for Canine Anal Furunculosis

Reference	Year Published	Oral Dosing	Pertinent Findings
Mathews et al[3]	1997	CsA (7.5–10 mg/kg q12h for 20 wk) 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[4]	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 wk. There was a 78% surface area reduction and 62% depth reduction after 4 wk of CsA therapy; these parameters worsened with administration of a placebo. 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[8,a]	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 occurred in 72%. The recurrence rate was 36% during follow-up (mean: 6.8 mo). Lesion recurrence averaged 10.6 wk after treatment ended.
Mouatt[9,a]	2002	CsA did not exceed 1 mg/kg q12h for 16 wk	100% of dogs showed >50% reduction in surface area and depth within 2 wk.

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

Reference	Year Published	Oral Dosing	Pertinent Findings
Mouatt[9,a] *(cont)*	2002	Ketoconazole (10 mg/kg q24h for 16 wk) Antibiotherapy was given for concurrent conditions.	100% of associated signs improved within 2 wk. Complete resolution occurred in 93% of dogs. 50% of dogs that had complete resolution were disease free for >1 yr. 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.
Patricelli et al[10,a]	2002	CsA (2.5 mg/kg q12h or 4 mg/kg q24h [duration not specified]) Ketoconazole (~8 mg/kg q24h in all dogs) There was no mention of concurrent antibiotherapy.	Resolution of associated clinical signs occurred within 9 wk in all dogs. Significant lesion improvement occurred in all dogs (mean time to remission: 14 wk). 63% of dogs that experienced remission had a mean time to recurrence of 12.4 wk. All dogs that experienced recurrence had moderate to severe disease at the initial examination.
Doust et al[6,a]	2003	CsA (1.5, 3, 5, or 7.5 mg/kg q24h for 13 wk) If clinical signs continued after 13 wk, owners could continue administering CsA. There was no mention of concurrent antibiotherapy.	Lesions and associated signs improved faster with the highest dose. The rate of complete resolution was higher in dogs administered the highest dose. A longer (>12 mo) remission or controlled response occurred regardless of the dose when dogs were treated for >13 wk. There was no consistent relationship between CsA blood concentration and efficacy.
O'Neill et al[14,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 associated clinical signs began in 1–2 wk. Lesions resolved in all dogs by 10 wk, but dramatic improvement occurred in the initial 2 wk. 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.

tributed to the study's results. Because of the wide safety margin, smaller dose used to treat canine anal furunculosis compared with allograft rejection, lack of definitive relationship between blood levels and efficacy, and reports in the literature, we do not routinely measure CsA trough blood levels. This diagnostic tool should be reserved for select patients, such as those receiving concurrent ketoconazole (see following paragraph), 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.[38,41] Unfortunately, this method is available in only select laboratories and is expensive.

duration of this therapy ranges from 8 to 16 weeks based on clinical improvement. 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. If ketoconazole is concurrently administered, it should be administered at a dose of 5 to 10 mg/kg/day PO to inhibit metabolism of CsA and thus reduce (by as much as 50% to 60%) the dose required for treatment. We prefer to initially administer CsA at a moderate once-daily dose (~5 mg/kg) with

Resolution of pain-related signs may be a satisfactory outcome for most owners, regardless of lesion improvement.

Coadministration of ketoconazole with CsA has been advocated to reduce the daily CsA dose and hence cost to clients.[9,10,14,42] 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.[41,42] 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. Clinicians should give their clients relevant information to help them decide whether to administer ketoconazole with CsA. Most other CsA-related drug interactions have been reported in humans.[37,41] Like ketoconazole, drugs known to affect cytochrome P-450 metabolizing enzymes (e.g., phenobarbital) may alter elimination of CsA.

Table 1 summarizes the results of treating canine anal furunculosis with CsA. Overall, it appears that a short course of high-dose CsA hastens the time to remission and longer CsA administration (at least ≥13 weeks) decreases the rate of relapse. The following recommendations are based on the discussion thus far, our interpretation of canine anal furunculosis clinical studies, and our experience. Other recommendations will likely be made in the future.

CsA appears to be the most effective medical treatment to date for canine anal furunculosis. We routinely administer CsA at a dose of 4 to 8 mg/kg/day PO. The ketoconazole to achieve the greatest possible response in the least amount of time and then taper the CsA dose and frequency of administration (to every 48 hours). This combined therapy is usually administered 6 to 12 weeks before tapering the CsA dose (beginning with a reduced daily dose is typical). As CsA tapering begins, topical tacrolimus should be coadministered (see following discussion). 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 CsA dose either reduced or discontinued pending CsA blood level results. Fortunately, we have rarely seen side effects suggestive of toxicosis.

Sulfasalazine has been used to treat humans with ulcerative colitis and Crohn's disease as well as in veterinary patients with the elusive IBD.[20,34,43] It can be dosed at 50 mg/kg/day divided q8–12h for dogs with IBD. This treatment alone has anecdotally helped patients with canine anal furunculosis. Because of potential idiosyncratic reactions and the risk of keratoconjunctivitis sicca, we do not use sulfasalazine to treat canine anal furunculosis.

Immunosuppressive or Immunomodulatory Therapy: Maintenance

Tacrolimus (previously known as *FK506*), another calcineurin inhibitor, has pharmacologic actions very

similar to those of CsA but is 10 to 100 times more potent[37,44,45] (Figure 5). It is applied topically to dogs because systemic administration requires careful drug monitoring.[46] All studies thus far indicate that significant levels of tacrolimus do not accumulate in the blood when it is given topically.[44,47,48] 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 (0.1%) has been reported to completely heal sinus tracts in 50% (i.e., 5 of 10) of dogs or noticeably improve lesions in 90% (i.e., 9 of 10) of dogs when applied once or twice daily to treat anal furunculosis.[13] 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. 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 (0.1%) has also been effective in treating canine discoid lupus erythematosus and pemphigus erythematosus.[47] Tacrolimus is not approved for use in dogs.

As induction therapy is tapered, topical tacrolimus (Protopic 0.1% ointment, Fujisawa Health Care) 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). Favorable results have been achieved by us and others.[49] 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

Antibiotherapy is recommended to control secondary infection, which is almost always present. 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 (Bactoderm, Pfizer) applied once or twice daily may help reduce bacterial colonization. Above all, it is important to keep the perianal region clean and dry. Clipping and cleaning the perianal region with chemical restraint can reduce purulent exudate, debride necrotic tissue, remove intralesional hair, and reduce pain. 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.

Dietary Therapy

In one report,[11] all 27 German shepherds with anal furunculosis had associated colitis as determined by clinical signs and colonic biopsy. Biopsies before administering glucocorticoids and feeding an alternative protein diet (i.e., lamb and rice and vegetarian dog foods) were characterized by mild to moderate fibrosis in the lamina propria in all dogs (i.e., 16 of 27) with attenuation of the superficial epithelium. Epithelial microerosions were present in a few cases. The inflammatory cell infiltration was predominantly composed of plasma cells and lymphocytes, with a few eosinophils in some cases. Eight to 16 weeks of therapy (i.e., glucocorticoids, change in diet) did not improve histopathologic colonic lesions compared with those before treatment.

Because we have successfully managed a few patients with mild canine anal furunculosis by administering antibiotics and feeding a restrictive trial diet without concurrently administering immunosuppressive agents, our opinion is that diet can influence the course of the disease. Food trials followed by dietary challenge would be beneficial in providing at least circumstantial evidence of a food-related component to canine anal furunculosis. Most owners are understandably unwilling to conduct a dietary challenge once their pet is free of clinical signs. If an association exists, the time from dietary challenge to formation of a new perianal tract is unknown.

MONITORING

Reexaminations are usually scheduled according to the type of therapy a patient is receiving. If the drugs being used do not require strict hematologic and biochemical monitoring, reexaminations every 3 to 5 weeks should be sufficient. 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, diarrhea, ribbon-like stool, increased frequency of defecation, perianal licking, self-mutilation, perianal pain, scooting, offensive odor, 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.[9]

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, chemical restraint is usually 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. Complete blood counts, serum biochemical profiles, and urinalyses can be conducted at the clinician's discretion based on historical findings, physical examination findings, and choice of therapy. Although CsA has not been associated with any major hematologic or biochemical alterations thus far in dogs, few long-term administration safety studies have been conducted. We generally conduct blood work monthly for the first 2 to 3 months, then as needed based on physical abnormalities detected during examination.[38] Urine cultures used to diagnose occult urinary tract infections are periodically conducted in patients receiving immunosuppressive agents.

A recent report described an 11-year-old, neutered German shepherd with anal furunculosis that was treated with CsA and ketoconazole.[50] After 4 weeks of therapy, the dog developed generalized lymphadenopathy and splenomegaly. Fine-needle aspiration showed cells characteristic of lymphoma. Although a causative relationship between the use of CsA and the development of lymphoma could not be proved, it is possible that CsA administration contributed to tumorigenesis. Because there is an increased risk of lymphoma development in humans receiving CsA, the same might be true in dogs.[50,51] To date, we have not diagnosed lymphoma in any dog treated with CsA, but this report stresses the importance of a complete physical examination during reexaminations to look for abnormalities suggestive of neoplasia.

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 sacculectomy. 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 our practice. Before using lasers, clinicians should become familiar with their advantages and disadvantages. Laser safety is a critical component of laser surgery. All personnel required during laser procedures should have completed a laser safety course. Laser-specific facemasks, wavelength-specific eyewear, smoke evacuators, surgical instruments, and laser-safe endotracheal tubes are required. Lasers are used to ablate and/or excise ulcerative necrotic tissue in patients with canine anal furunculosis.[52] We specifically use lasers to remove the epithelial lining of sinus tracts, sterilize the wound bed, and decrease patient discomfort. During the procedure, either the patient has saline-soaked gauze inserted into its rectum or its anus is closed with a pursestring suture to prevent combustion. Rectal enemas are occasionally needed before surgery. Enemas are also beneficial for patients that are constipated or obstipated.

FUTURE TREATMENTS

To achieve and maintain remission in humans with Crohn's disease, several new and emerging therapeutic options are being used.[17] Many of these agents are designed to precisely block or enhance immunologic events (i.e., cell signaling, leukocyte adhesion) believed to be involved in the pathogenesis of Crohn's disease. Specifically, monoclonal anti–TNF-α antibodies (i.e., infliximab, cytidine diphosphate-571), 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.[17] Perhaps once the veterinary community elucidates the immunopathogenesis of canine anal furuncu-

losis, similar specific immune-altering therapies may prove useful in managing the disease.

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ARTICLE #1 CE TEST

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1. Which disease does canine anal furunculosis most resemble in humans?
a. Chediak–Higashi syndrome
b. Vogt–Koyanagi–Harada syndrome
c. Stevens–Johnson syndrome
d. none of the above

2. Which clinical signs do not typically occur in patients with canine anal furunculosis?
a. hematochezia and dyschezia
b. frequent defecation and diarrhea
c. dehydration and vomiting
d. tenesmus and self-mutilation

3. Which zone of the anus contains hepatoid glands?
a. columnar
b. intermediate
c. reticularis
d. cutaneous

4. The external anal sphincter is
a. voluntary smooth muscle.
b. voluntary striated muscle.
c. involuntary smooth muscle.
d. involuntary striated muscle.

5. Cytology of sinus tracts most commonly reveals
a. pyogranulomatous inflammation.
b. eosinophilic inflammation.
c. a mixed bacterial population.
d. a and c

6. Anal stenosis and fecal incontinence are potential complications of
a. deroofing and fulguration.
b. cryotherapy.
c. surgical excision.
d. all of the above

7. Which statement(s) regarding CsA is correct?
a. The microemulsion form of CsA is the most bioavailable.
b. Absorption of CsA is enhanced with food.
c. Inhibitors of cytochrome P-450 metabolizing enzymes decrease CsA blood levels.
d. a and c

8. Which adverse effect(s) does not appear to occur when CsA is administered at routine doses?
a. vomiting and diarrhea
b. increased hair shedding
c. nephrotoxicity
d. gingival hyperplasia

9. Which statement regarding tacrolimus is incorrect?
a. Tacrolimus, like CsA, is a calcineurin inhibitor.
b. Tacrolimus is approved for use in dogs.
c. Topical tacrolimus significantly accumulates in the bloodstream.
d. b and c

10. German shepherds commonly appear to have _____ in conjunction with canine anal furunculosis.
a. pancreatitis
b. otitis
c. colitis
d. prostatitis