

The prevalence of bacterial infections during cyclosporine therapy in dogs: A critically appraised topic

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Abstract — Cyclosporine is used to treat immune-mediated and allergic conditions and to prevent transplant rejection. To determine the prevalence of bacterial infections during cyclosporine therapy in dogs, 2 databases were searched and 14 articles reporting usable data were identified. In 828 dogs with atopic dermatitis receiving anti-allergic dosages of cyclosporine, the prevalence of bacterial infections was 11%; these occurred most often in the integument and urinary systems and not in multiple systems. In 95 dogs receiving cyclosporine at higher dosages for other conditions, the prevalence of bacterial infection was 17%, and these infections occurred most often in the gastrointestinal, urinary, and respiratory systems, often occurring at more than one body site. The prevalence of bacterial infections in atopic dogs treated with cyclosporine is low and occurs most often in the skin. When given for immunosuppression, the prevalence of bacterial infections is higher and can affect one or more body systems.

Résumé — Prévalence d'infections bactériennes durant la thérapie à la cyclosporine chez les chiens : un sujet évalué de manière critique. La cyclosporine est utilisée pour traiter des conditions allergiques et à médiation cellulaire et également pour prévenir le rejet de greffe. Afin de déterminer la prévalence d'infections bactériennes durant la thérapie à la cyclosporine chez le chien, deux bases de données furent recherchées et 14 articles rapportant des données utilisables furent identifiés. Chez 828 chiens avec une dermatite atopique recevant des dosages anti-allergiques de cyclosporine, la prévalence d'infections bactériennes était de 11 %; celles-ci survenaient le plus souvent dans les systèmes tégumentaire et urinaire mais pas dans des systèmes multiples. Chez 95 chiens recevant de la cyclosporine à des dosages plus élevés pour d'autres conditions, la prévalence d'infections bactériennes était de 17 %, et ces infections survenaient le plus souvent dans les systèmes gastro-intestinal, urinaire et respiratoire, se rencontrant souvent dans plus d'un site corporel. La prévalence d'infections bactériennes chez des chiens atopiques recevant de la cyclosporine est faible et survient le plus souvent au niveau de la peau. Lorsqu'administrée pour immunosuppression, la prévalence d'infections bactériennes est plus élevée et elles peuvent affecter un ou plus d'un système du corps.

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Introduction

Cyclosporine is an immunomodulating drug that suppresses the expression of immunostimulating cytokines (e.g., interleukin-2 and interferon-gamma) in activated T-lymphocytes and other immune cells (1). This immunosuppressant has been used for decades in human and veterinary medicine for the treatment of immune-mediated and allergic conditions and to prevent renal allograft transplant rejection (1). In the dog, several adverse events have been associated with the use of cyclosporine, including vomiting, diarrhea, gingival hyperplasia, papillomatous skin lesions, and infections (1,2). The develop-

ment of cyclosporine-induced bacterial infections can predispose patients to a higher risk of morbidity or mortality. A more precise knowledge of the prevalence of bacterial infections during cyclosporine treatment and of the factors influencing infection development could aid veterinarians in detecting and treating infections earlier; such knowledge would also be helpful to better inform pet owners during decision-making for treatment.

The veterinary literature was searched to identify the prevalence of bacterial infections in dogs treated with cyclosporine for any disease. Possible factors that could contribute to the development of these bacterial infections were also searched. For

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Table 1. Prevalence of bacterial infections in A, dogs with atopic dermatitis (AD) (8 articles, 828 dogs) and B, dogs with other conditions (6 articles, 95 dogs).

Reference number	Primary author	Year	Disease treated	Total number of dogs (T)	Number of dogs with a bacterial infection (N)	Prevalence (N/T, %)
A: Dogs with atopic dermatitis						
21	Olivry	2002	AD	61	3	5%
22	Steffan	2003	AD	117	29	25%
4	Burton	2004	AD	41	4	10%
23	Steffan	2005	AD	266	25	9%
24	Radowicz	2005	AD	51	7	14%
14	Dip	2013	AD	48	8	17%
29	Little	2015	AD	112	13	12%
30	Moyaert	2017	AD	132	1	1%
			Total	828	90	11%
B: Dogs with other conditions						
20	Mouatt	2002	AF	16	1	6%
5	Gregory	2006	RT	15	4	27%
25	Schmiedt	2006	RT	8	5	63%
13	Adamo	2007	MUE	10	3	30%
27	Hopper	2012	RT	26	2	8%
16	Rhoades	2016	IMPA	20	1	5%
			Total	95	16	17%

AF — Anal furunculosis/perianal fistulae; IMPA — Immune-mediated polyarthritis; MUE — Meningoencephalomyelitis of unknown etiology; RT — Renal transplantation.

the evidence search and assessment, the methodology of critically appraised topics was used, as described recently (3), as were the headings proposed on www.bestbetsforvets.org/about-bets

Materials and methods

Clinical scenarios

The first scenario is a 5-year-old spayed female West Highland white terrier (WHWT) with atopic dermatitis (AD). There was a minimal improvement of clinical signs during treatment with previously administered therapies, and now therapy with cyclosporine at the approved dosage of 5.0 mg/kg body weight (BW) per day has been elected. The owner is concerned because she just browsed the Internet and found that cyclosporine is an immunosuppressant that could cause potentially severe bacterial infections. The owner asks how often dogs treated with this medication develop bacterial infections and what type of infections usually occur.

The second scenario is a 7-year-old castrated male Labrador retriever dog with immune-mediated polyarthritis (IMPA). The dog's condition is in remission, and managing long-term with cyclosporine is being considered. If a cyclosporine dosage of 10.0 mg/kg BW per day is administered, would the risk of bacterial infections in this pet differ from that in the WHWT, given the higher cyclosporine dosage.

Structured question

The aim was to answer the same question in 2 different dog populations:

What is the prevalence of bacterial infections in:

1. Dogs with AD treated with oral cyclosporine at the approved starting anti-allergic oral dosage of 5 mg/kg BW per day; and
2. Dogs with other conditions treated with oral cyclosporine at immunosuppressive dosages greater than 5 mg/kg BW per day.

Literature search

The Web of Science (Science Citation Index Expanded) and CAB abstract databases were searched for relevant articles on August 25, 2018 and November 2, 2019, using the following search string: (dog or dogs or canine) AND (cyclosporin* or cyclosporine) AND [*bacteri* AND (infect* OR pyoderma OR skin OR urinary OR nephritis OR cystitis OR kidney OR bladder OR pneumonia OR lung OR meningitis OR encephalitis OR brain OR meninge*)]. The search was limited to articles published since 2000, the time around which the oral modified cyclosporine became commercially available for use in dogs. The bibliographies of identified articles were then searched for additional relevant articles. Review articles were excluded due to the interest in original reports. Meeting abstracts were not searched because detailed information was needed.

The query identified 38 and 180 citations in the Web of Science and CAB abstracts, respectively. Fifteen articles reporting usable data were selected: 9 from the Web of Science (4–12) and 6 from the CAB Abstracts (13–18). Additionally, 12 articles were identified from screening the bibliography of previously selected articles (19–30). Finally, 1 article that was published between the 2 searches was added (31).

To avoid a publication bias, case reports detailing rare or unusual infections were not included in the final assessment; therefore, 12 articles were excluded (6–9,11,12,15,17,18,26,28,31) and the remaining 16 articles were evaluated (4,5,10,13,14,16,19–25,27,29,30).

Finally, upon further review, 2 articles were eliminated, as one did not specifically differentiate infections between atopic dogs and those with other conditions (10), while the other did not specify the number of dogs with infections (19).

In addition to the overall prevalence and body location of bacterial infections, some of the potential factors that could have influenced the development of infection were investigated,

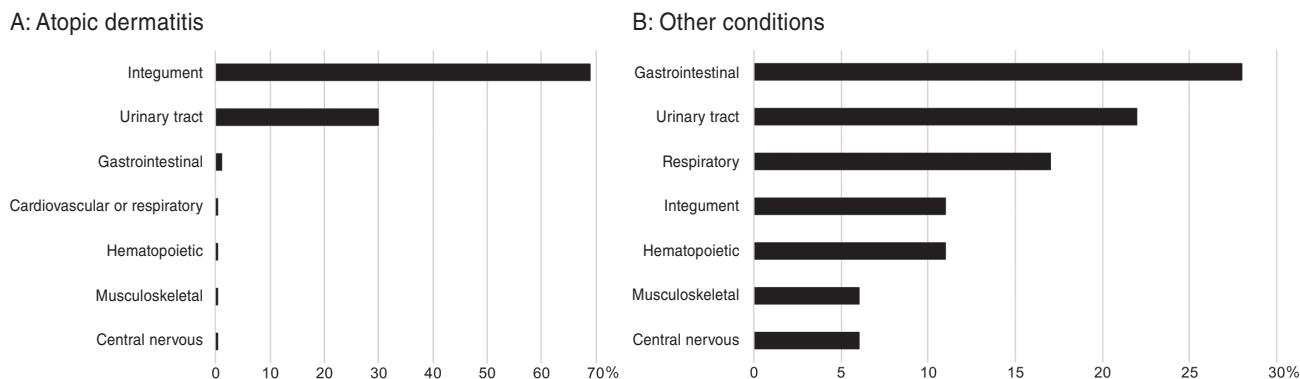


Figure 1. Frequency of infection of body systems in A – dogs with atopic dermatitis (AD), and B – dogs with other conditions.

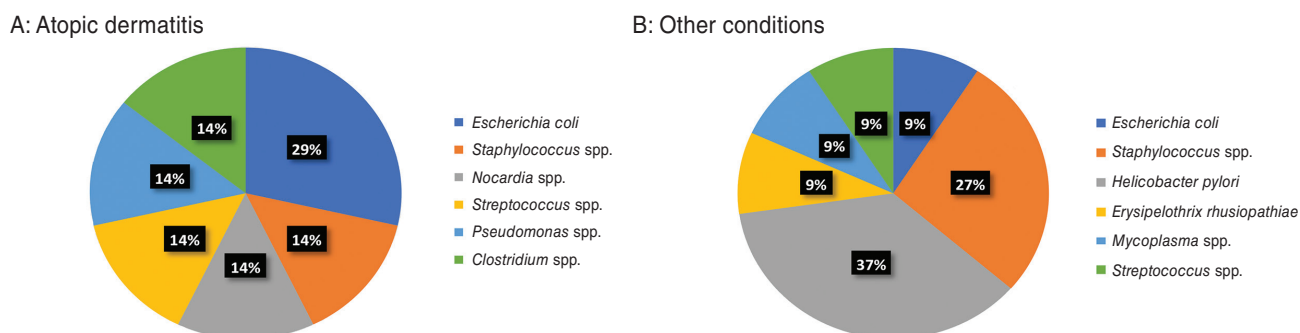


Figure 2. Frequency of bacterial genera isolated from dogs treated with ciclosporin. A – dogs with atopic dermatitis (AD); B – dogs with other conditions.

where available. These parameters were: the dosage and the frequency of cyclosporine administration, the disease treated with cyclosporine, the dosages and frequencies of concurrently administered medications, the type of bacteria isolated, the time to the appearance of infection, and any other factors that could potentially contribute to the development of infections.

Results

Relevant data extracted from each of the 16 selected articles are found in Appendix 1.

Dogs with atopic dermatitis

Eight articles were identified describing dogs with AD that had developed bacterial infections during treatment with cyclosporine (4,14,21–24,29,30).

Prevalence of bacterial infections

Altogether, 90/828 atopic dogs treated with cyclosporine were reported to have developed bacterial infections; a prevalence of 11% (Table 1A).

Types of bacterial infections

The localization of the identified bacterial infections in atopic dogs is depicted in Figure 1A. None of the dogs developed an infection in more than 1 body system, but at least 1 dog in each study developed a skin infection. The most affected system was the integument (61/90 dogs, 68%). Among these

61 dogs with skin infections, there were 60 dogs with pyoderma, bacterial folliculitis, or pyotraumatic dermatitis (98%; 67% of all infections) and 1 dog with granulomatous skin lesions associated with *Nocardia* spp. (2%; 1% of all infections). The second most commonly affected system was the urinary tract (27/90 dogs; 30%) with all 27 dogs diagnosed with bacteriuria and only 1 exhibiting clinical signs of urinary tract infection (23). One article reported 9 dogs with evidence of bacteriuria both before and after cyclosporine therapy; these dogs were excluded from the final count of dogs with bacteriuria (23). The only other body system affected in atopic dogs was the gastrointestinal tract, with 1 dog diagnosed with bacterial enteritis (23).

Isolated bacteria

Seven bacterial isolates were identified in 2 of 8 articles (Figure 2A). In 2 dogs (29%), *Escherichia coli* was cultured, and the remaining 5 species (*Staphylococcus* spp., *Nocardia* spp., *Streptococcus* spp., *Pseudomonas* spp., and *Clostridium* spp.) were identified in 1 dog each (14%). Five of seven isolates (71%; *Escherichia coli*, *Staphylococcus* spp., *Nocardia* spp., *Streptococcus* spp., *Pseudomonas* spp.) were found in the urine, 1 (14%; a *Clostridium* spp.) was cultured from the gastrointestinal tract, and 1 (a *Nocardia* spp.) was grown from a deep cutaneous granuloma. The relatively low reporting of staphylococcal bacteria isolated is likely due to that species not being cultured or identified explicitly in 83/90 skin infections (92%).

Time to development of infection

None of the studies describing the treatment of dogs with AD reported the time to development of bacterial infection in the affected patients.

Cyclosporine dosage and concurrent medications

The dosages of cyclosporine were extractable from all 8 selected articles, and are summarized in Appendix 1. These dosages ranged from 2.5 to 6.6 mg/kg BW per day with most articles (5/8, 63%) reporting dogs receiving an average dosage of 5 mg/kg BW per day; 1 trial allowed tapering the dosing to every other day (23). The dogs that developed an infection at locations other than the skin had been prescribed the same dosage (5 mg/kg BW per day) as that given to most dogs with AD. Thus, it seems that the dosage of cyclosporine did not influence the location of bacterial infections in atopic dogs.

The concurrent use of another medication was reported in only 1 trial (14) in which 1 dog treated with cyclosporine and prednisolone at 1 mg/kg BW per day developed a bacterial skin infection. In that article, another dog treated solely with cyclosporine was also reported as having a bacterial skin infection while 6 others had an unspecified pyoderma (14).

Dogs with other conditions

Six articles describing infections in dogs treated with cyclosporine as an immunosuppressant were reviewed (5,13,16, 20,25,27). In these articles, this drug was used to manage immune-mediated polyarthritis (16), anal furunculosis (20), meningoencephalomyelitis of unknown etiology (13), or immunosuppression after renal transplantation (5,25,27).

Prevalence of bacterial infections

Altogether, 16/95 dogs (a prevalence of 17%) developed bacterial infections while undergoing cyclosporine therapy for immune-mediated conditions or after renal transplantation (Table 1B).

Types of bacterial infections

The localization of the bacterial infections reported in dogs with immune-mediated conditions or after renal transplantation is depicted in Figure 1B. As 2/16 dogs (13%) had developed an infection at more than 1 body site (5), there was a total of 18 infections. Among these dogs with multiple infections, one had a bacterial septicemia suspected to be secondary to a chronic pyoderma and the other had a septic pleuritis and meningitis. Altogether, the affected body systems were, in descending order of frequency, the gastrointestinal tract (5/18, 28%), the urinary system (4/18, 22%), respiratory system (3/18, 17%), hematopoietic and integumentary systems (2/18 each, 11%), and musculoskeletal and nervous systems (1/18 each, 6%).

Isolated bacteria

Eleven bacterial isolates were identified in 8 dogs in 3 articles (Figure 2B) (5,16,25). In 1 dog, 2 bacterial species were isolated and in one, 3 species were grown. The most identified bacterial species was *Helicobacter pylori* (4 isolates, 37%), all cultured from the gastrointestinal tract. The second most

common bacterial genus was *Staphylococcus* spp. (3 isolates, 27%), and these bacteria were isolated from the urinary tract, the integument, and the pleura/meninges in 1 dog each. The remaining 4 isolates were identified in 1 dog each (9%), and they were found in the integument (*E. coli* and *Streptococcus* spp.), the pleura/meninges (*Mycoplasma* spp.), and the blood (*Erysipelothrix rhusiopathiae*).

Time to development of infection

The time to development of bacterial infection following the initiation of cyclosporine therapy was reported in 4 articles (7 dogs; Appendix 1) (5,16,20,27). These articles described a time to infection varying between 8 and 264 d, with a median time to infection of 18 d.

Cyclosporine dosage and concurrent medications

The dosages of cyclosporine were extractable from all 6 selected studies, and they are summarized in Appendix 1. The dosages used for the management of immune-mediated diseases or the prevention of renal transplant rejection ranged from 2.2 to 24.0 mg/kg BW per day with 4 articles reporting at least 1 dog treated with a dosage of cyclosporine of 20 mg/kg BW per day or greater. The dogs that developed a bacterial infection in more than one body site were receiving 20 mg/kg BW per day of cyclosporine (5).

Only 1 article reported the use of cyclosporine monotherapy for the management of IMPA (16). The remaining 5 articles all described the use of concurrent medications. A potentiation of the pharmacokinetics of cyclosporine with ketoconazole was stated in 3 articles for 7 dogs (13,20,25) including 1 that reported a cyclosporine dosage less than 5 mg/kg BW per day (20). The other added immunosuppressive medications were glucocorticoids (13 dogs) (5,13,25,27), azathioprine (6 dogs) (5,27), capecitabine (5 dogs) (25), and leflunomide (2 dogs) (27).

Discussion

Limitations of our analysis was the relative lack of detail about the type of infection identified in dogs treated with cyclosporine. Numerous articles that could have been added herein merely stated the word "infection" as an adverse event. One could thus not assume that the infection was bacterial; it was suspected that some dogs with bacterial infections were not accounted for. Another limitation was that over half of the articles did not identify the specific bacteria isolated, which may have falsely under- or over-represented some bacterial species. When reporting the diagnosis of "pyoderma," the depth of infection was typically not stated. As dogs with AD appear predisposed to develop bacterial skin infections (32), the role played by cyclosporine in the spread of these pyodermas is unclear, especially as the specific prevalence of pyoderma development in dogs with AD has not been established. Furthermore, most articles did not differentiate true infections from mere bacterial contamination or colonization. Although bacteria were isolated in each case, one cannot assume that the bacteria were inducing the disease. A good example of this is that only 1 dog of the 27 with bacteriuria exhibited clinical signs of UTI. Additionally, a

positive culture for *Helicobacter pylori* was obtained in 4 dogs, but another article showed no correlation between high numbers of *Helicobacter* spp. and true gastritis in dogs (33). In future studies, and to avoid confusion, efforts should be made to better differentiate infections from contaminations or colonizations, for example by reporting the presence of phagocytized bacteria and describing clinical signs of infection in greater details. Finally, several studies described the use of a combination of drugs to immunosuppress dogs, for example, for the prevention of renal transplant rejection. As a result, it is unclear if the infections observed were caused by the cyclosporine, the added immunosuppressants, or the combination thereof.

In summary, the prevalence of bacterial infections in atopic dogs treated with cyclosporine is approximately 11% while that in dogs treated for other immune-mediated conditions or after renal transplantation is approximately 17%.

In dogs with AD, bacterial infections most often occurred in the integument and urinary systems, which should prompt the monitoring of these sites for clinical signs of infection during treatment. Confounding issues are that AD, by itself, can predispose dogs to secondary bacterial skin infections and that bacteriuria can be present in the absence of dysuria, which might have arisen before cyclosporine therapy was initiated. The treatment of dogs with cyclosporine at dosages of ≤ 5 mg/kg BW per day appears not to predispose the dogs to developing infections at multiple body sites. In contrast, in dogs receiving cyclosporine for the treatment of immune-mediated diseases or after renal transplantation, infections can occur in various body systems, and they might be present at more than one body site. The most affected systems are the gastrointestinal, urinary, and respiratory systems. The median time to development of infection was 18 d. It could not be determined if the higher cyclosporine dosage contributed to bacterial infection development because of the concurrent use of additional immunosuppressive drugs in most dogs.

Additional studies are needed to establish more accurately the prevalence of bacterial infections in dogs treated with cyclosporine, and to identify specific factors influencing the development of such infections. Patients enrolled in such studies should be screened for pre-existing infections and excluded whenever one is identified. Detailed information about the bacterial infections should be recorded, including the location of the infection, the identification of bacterial species, and the time at which the infection occurred in relation to the initiation of cyclosporine (or other) therapy. Where possible, concurrent immunosuppressive medications should be excluded in order to more precisely identify the role of cyclosporine in the development of these infections.

Finally, the prevalence, clinical type, and bacteria involved in pyoderma should be established in dogs with AD in the absence of anti-allergic therapy, for example, in clinical trials with a placebo arm. Such data will help determine if any of the immuno-modulating drugs used for AD have an explicit role in predisposing the dogs to develop skin and other infections.

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Appendix 1. Summary of extracted data.

Reference number	Author	Year	Total number of dogs	Cyclosporine dosage (frequency)	**Concurrent medications; dosage (frequency)	Length of time on cyclosporine (days)	Disease treated	Total number of dogs with infections	Type of bacterial infection	Bacteria isolated
A: Dogs with atopic dermatitis										
21	Olivry	2002	61	2.5 mg/kg [1] or 5.0 mg/kg [2] (daily)	Not applicable	Not specified	AD	3	Pyoderma or Pyotraumatic dermatitis	Not specified
22	Steffan	2003	117	4.6 mg/kg (daily, then tapered)	Not applicable	Not specified	AD	29	Pyoderma, Pyotraumatic dermatitis	Not specified
4	Burton	2004	41	4.2 to 5.0 mg/kg (daily)	Not applicable	Not specified	AD	4	Pyoderma	Not specified
23	Steffan	2005	266	5.0 mg/kg (daily then every other day)	Not applicable	Not specified	AD	25	Enteritis [1]; Granulomatous skin lesion [1]; bacteriuria [23]	<i>Nocardia</i> spp. (1), <i>Clostridium</i> spp (1), rest not specified
24	Radowicz	2005	51	5.0 mg/kg (daily)	Not applicable	Not specified	AD	7	Bacteriuria [4]; bacterial skin infection [3]	Bacteriuria: <i>Staphylococcus pseudintermedius</i> (1), beta-haemolytic <i>Streptococcus</i> (1), <i>Escherichia coli</i> (2) and <i>Pseudomonas aeruginosa</i> (1)

Appendix 1. Summary of extracted data (*continued*).

Reference number	Author	Year	Total number of dogs	Cyclosporine dosage (frequency)	**Concurrent medications; dosage (frequency)	Length of time on cyclosporine (days)	Disease treated	Total number of dogs with infections	Type of bacterial infection	Bacteria isolated
A: Dogs with atopic dermatitis										
14	Dip	2013	48	5.0 mg/kg (daily)	Prednisolone, 1 mg/kg (daily, then every other day) [1]	Not specified	AD	8	Bacterial skin infection [2]; pyoderma [6]	Not specified
29	Little	2015	112	3.2 to 6.6 mg/kg (daily)	Not applicable	Not specified	AD	13	Pyoderma	Not specified
30	Moyaert	2017	132	5.0 mg/kg (daily)	Not applicable	Not specified	AD	1	Bacterial skin infection	Not specified
B: Dogs with other conditions										
20	Mouatt	2002	16	2.2 mg/kg ^a (daily)	Ketoconazole, 10 mg/kg (daily)	140	AF	1	Septic Arthritis	Not specified
5	Gregory	2006	15	20.0 mg/kg (daily)	Azathioprine, 2 to 3 mg/kg (every other day); methylprednisolone, 10 mg/kg (single dose); prednisolone, 1 mg/kg (daily)	10 to 270	RT	4	Septic pleuritis/ meningitis [1]; septic peritonitis [1]; pneumonia [1]; pyoderma and septicemia [1]	<i>Staphylococcus</i> spp./ <i>Mycoplasma</i> spp. [1]; hemolytic <i>Staphylococcus</i> spp./ <i>Escherichia coli</i> /gamma- <i>Streptococcus</i> spp. [1]; others not specified
25	Schmiedt	2006	8	8.0 mg/kg (daily)	Capecitabine, 500 mg/m ² ^a (daily); ketoconazole 10 mg/kg (daily); prednisolone 0.5 mg/kg (daily)	Not specified	RT	5	UTI [1]; gastritis/Enteritis [4]	Beta-hemolytic, coagulase-positive <i>Staphylococcus</i> spp. [1]; <i>Helicobacter pylori</i> [4]
13	Adamo	2007	10	6.0 to 24.0 mg/kg (daily)	Glucocorticoids, not specified [2]; ketoconazole, 8 mg/kg (daily) [1]	Not specified	MUE	3	UTI	Not specified
27	Hopper	2012	26	20.0 mg/kg (daily)	Prednisolone, 1 mg/kg (daily); azathioprine, 2 to 3 mg/kg (every other day) or leflunomide, 4 to 6 mg/kg (daily)	14; 264	RT	2	Bacterial pneumonia [1]; pyoderma [1]	Not specified
16	Rhoades	2016	20	10.0 mg/kg (daily)	Not applicable	75	IMPA	1	Bacteremia	<i>Erysipelothrix rhusiopathiae</i>

** Medications known to alter the metabolism of ciclosporin.

^a Mean dose.

[] — Number of dogs; AD — Atopic dermatitis; AF — Anal furunculosis/perianal fistulae; IMPA — Immune-mediated polyarthritis; MUE — Meningoencephalomyelitis of unknown etiology; RT — Renal transplantation; UTI — Urinary Tract Infection.

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