

Evaluation of *Lactobacillus rhamnosus* strain GG for the prevention of atopic dermatitis in dogs

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Objective—To evaluate the efficacy of the probiotic *Lactobacillus rhamnosus* strain GG for the alleviation or prevention of clinical signs of atopic dermatitis (AD) in genetically predisposed dogs.

Animals—2 adult Beagles with severe AD and 16 puppies.

Procedures—The 2 adult Beagles were bred twice, with a year between breedings. *Lactobacillus rhamnosus* GG was administered to the bitch during the second pregnancy and to the puppies of the second litter from 3 weeks to 6 months of age. Both litters were epicutaneously sensitized to *Dermatophagoides farinae*. Blood samples were collected from puppies every 6 weeks to measure serum titers of allergen-specific IgE. At 6 months of age, all puppies underwent intradermal allergen testing and environmental challenge with *D farinae*. Clinical signs were scored.

Results—In the first litter, at 6 months of age, 7 of 7 puppies were strongly seropositive for IgE against *D farinae*, 6 had a positive reaction to intradermal testing, and 7 developed severe clinical signs of AD after the environmental challenge. In the second litter, 7 of 9 puppies were seropositive, 3 had a positive reaction to intradermal testing, and 6 developed dermatitis and pruritus after the challenge. The second litter had a significantly lower serum titer of allergen-specific IgE and milder reaction to intradermal testing, compared with the first litter. Clinical scores did not differ between litters.

Conclusions and Clinical Relevance—Administration of *L rhamnosus* GG to puppies appeared to reduce immunologic indicators of AD, although no significant decrease in clinical signs was detected. (*Am J Vet Res* 2009;70:735–740)

Atopic dermatitis is reportedly the second most common allergy in dogs.¹ Although the prevalence of AD varies depending on the diagnostic criteria and geographic location,² the prevalence of AD in dogs may be increasing. Results in a 1971 report³ suggested that the prevalence at that time was as low as 3.3%, whereas results in a 1989⁴ report suggested that AD affected approximately 27% of dogs.

Dogs can be genetically predisposed to developing AD,⁵ and a predilection within certain breeds of dogs has been reported.^{3,6–8} The clinical course of AD is typically progressive. Most available treatments (eg, glucocorticoid drugs and cyclosporine) are used to modulate the existing inflammation.¹ In humans, the only treatment that possibly affects the course of disease is allergen-specific immunotherapy.⁹ Because immunotherapy involves long-term administration of injections, this form of treatment is not always acceptable to dog owners.

The chronic nature of the disease and the development of secondary infections, which can significantly increase the severity of clinical signs, have a considerable impact on the quality of life of affected dogs and their owners. Because AD is chronic, progressive, and

ABBREVIATIONS

AD	Atopic dermatitis
CADESI	Canine Atopic Dermatitis Extent and Severity Index
LGG	<i>Lactobacillus rhamnosus</i> strain GG
Th	T-helper

prevalent, identification of methods to prevent or reduce the clinical signs of disease in affected dogs would be of great benefit.

Probiotics are living microorganisms that, when ingested in a certain amount, provide health benefits beyond basic nutrition.^{10,11} The exact mechanism by which probiotics influence the development of AD has not been fully elucidated, but the proposed mechanism is modulation of the immune response toward a Th1 cell-mediated response.^{12–14} Improvement in clinical signs in atopic children receiving probiotics is associated with a significant increase in the Th1-cell interferon- γ response to the allergen and altered responses of Th1 cells to skin and enteric flora.¹⁵ This effect is long lasting and is still evident 2 months after administration of probiotics ceases.

Probiotics are typically strains of gram-positive lactobacilli or bifidobacteria and streptococci,¹⁶ and the beneficial effects are highly dependent on the particular strain used.^{17–19} Results of the limited studies^{20,21} of probiotics in dogs suggest that there are

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several promising probiotics for treatment of dogs. Although LGG is a human strain, it has the ability to survive gastrointestinal transit in dogs.²² To the author's knowledge, the clinical efficacy of probiotics for the prevention or treatment of AD in dogs has not been explored.

An experimental model of AD in dogs has been established in a colony of Beagles with a high serum concentration of allergen-specific IgE.^{23–27} These dogs were epicutaneously sensitized to *Dermatophagoides farinae* (house dust mites) and developed pruritic dermatitis after exposure to *D farinae* that was clinically, histologically, and immunologically similar to AD. The purpose of the study reported here was to evaluate the ability of LGG to prevent the development of AD in genetically predisposed Beagles that were sensitized to and challenged with an allergen of reference (*D farinae*) and to decrease the severity of clinical signs in dogs that developed AD. An additional purpose was to investigate the effects of oral administration of LGG on the amount of circulating and cutaneous allergen-specific IgE. The hypotheses tested were that prenatal administration of LGG would decrease the severity of clinical signs in Beagles highly predisposed to developing AD and modulate the response to allergen exposure by decreasing the synthesis of allergen-specific IgE.

Materials and Methods

Animals and housing—One male and 1 female belonging to a colony of Beagles with a high serum titer of IgE against *D farinae* (ie, > 3,000 ELISA antigen units, when values > 150 were considered a positive result^a) were used. Both dogs were severely atopic and had been epicutaneously sensitized to *D farinae*. They were known to consistently develop severe pruritus and dermatitis after allergen exposure via inhalation, epicutaneous contact, or oral administration.^{26,27} The intradermal injection of *D farinae*^b (25 protein nitrogen units/mL) yielded a 4+ reaction 15 minutes after injection (0 = score for injection of saline [0.9% NaCl] solution and 4+ = score for injection of histamine).

To minimize the influence of potential confounding factors on the results, the dogs were bred twice, 1 year apart, at the same time of year. The breeding was natural, and pregnancy was confirmed via ultrasonographic examination. The 2 adults and the puppies that originated from the 2 breedings were housed in controlled environmental conditions (consistent temperature and humidity, with no access to outdoors) and fed the same age-appropriate diet^{c,d} throughout the study. Dogs were housed in cement runs that were washed daily with high-temperature and -pressure washers (water and bleach). Air filters were changed routinely. Stuffed toys, carpets, and soft bedding that could trap dust were not allowed in the runs. An allergen detection system^e was used to test walls and filters monthly to ensure that the amount of *D farinae* in the environment was less than the detection limit of the test between challenges. The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Florida.

Probiotics choice and protocol—The suggested daily dose for LGG in dogs ranges from 50×10^9 CFUs to 500×10^9 CFUs.²³ One capsule of the commercial product^f used in this study contains a minimum of 20×10^9 CFUs. From this information, it was calculated that a suitable dose for an adult dog would be between 3 to 25 capsules/d.

When the bitch was pregnant with her first litter, she did not receive LGG; the offspring from this pregnancy were considered the control litter. During the second pregnancy, LGG was administered to the bitch at a dosage of 10 capsules/d, starting at week 3 of gestation and continuing throughout lactation. The offspring from the second pregnancy (LGG litter) received 5 capsules/d, starting at 3 weeks of age (as soon as they could eat some solid food), and this treatment continued until 6 months of age. Although the study was performed in controlled conditions, the investigator was aware of the treatments the puppies had received.

Sensitization protocol for the puppies—To prepare the allergen for use, 1 g of pure (> 99%) whole-bodied, naturally milled *D farinae*^b was mixed with 2.5 mL of sterile saline solution to create a thick paste with an allergen concentration of 400 mg/mL. Starting when both groups of puppies were 3 weeks of age, 0.3 mL (120 mg/dose) of the allergen paste was applied with a soft brush over small areas of untreated skin of the axillary and inguinal regions twice weekly for 12 weeks. Site of application was rotated (ie, application to both sites on 1 side of the body, then application to the contralateral inguinal and axillary regions) so that each site received an application every fourth time.

Serologic evaluation—To monitor the development of sensitization and an immunologic response to the *D farinae* allergen, a blood sample (0.5 mL) was obtained from each puppy every 6 weeks, starting at approximately 6 weeks of age until 6 months of age. Serum was harvested and submitted to a private laboratory for detection of IgE against *D farinae* (an ELISA antigen unit value > 150 was considered a positive result). The laboratory was unaware of the assignment of puppies to treatment groups.

Intradermal allergen testing—At 6 months of age, all puppies underwent testing for skin reaction to intradermal injection of *D farinae*. One intradermal injection each of 0.05 mL of saline solution (negative control test), histamine (positive control test), and *D farinae* at various concentrations (1:5,000 [wt/vol], 1:25,000 [wt/vol], and 1:100,000 [wt/vol]) was administered. After 15 minutes, skin reactions were subjectively evaluated and scored on a scale from 0 to 4 (0 = score for saline solution and 4+ = score for histamine). Syringes of intradermal testing solutions were coded, and identities of the solutions were determined only after completion of all the evaluations to prevent investigator bias. Reactions scored as 2 or higher were considered a positive test result.

Allergen challenge—At 6 months of age, all puppies were environmentally challenged with *D farinae* as described elsewhere.^{26,27} Briefly, a solution of *D farinae* was prepared from *D farinae*^b mixed with filtered saline

solution (pH, 7.2) to obtain a final concentration of 31 mg/mL. Prior to use, the solution was mixed with a vortex machine and sonicated. It was then applied (50 mg of *D farinae*/challenge) on the floor of a plastic portable dog kennel. Each dog was placed in the kennel for 3 h/d for 3 consecutive days. Kennels were washed at the end of the challenge. The concentration and volume of *D farinae* used were selected on the basis of data from other studies.^{26,27}

Clinical signs of AD were evaluated by use of a modified CADESI scoring system²⁸ before and 6 hours after the beginning of each exposure to *D farinae*, and every 24 hours afterward, for a total of 5 days. The body of each dog was evaluated in small sections, each of which received a score on the basis of the clinical signs detected. The total score was calculated by summing the scores of all clinical signs and body sites, and this total score was used in the statistical analyses. Clinical signs of AD included diffuse erythema, erythematous macules, papules, excoriations, and alopecia. The scoring system ranged from 0 (absent) to 3 (severe) for each site and each sign. At the end of the challenge, the investigator performed an overall evaluation of the severity of AD and subjectively identified puppies considered clinically affected.

Statistical analysis—Statistical analysis was performed by use of statistical software.^h Analyses of variance were used to compare CADESI scores for AD, serum titers of IgE against the allergen, and results of intradermal allergen tests between the 2 litters. Unpaired *t* tests were used to compare values for the 3 variables at each time point. The Pearson product correlation test was used to evaluate potential correlations between serum titers of allergen-specific IgE and CADESI scores. A value of $P < 0.05$ was considered significant.

Results

Animals—The bitch conceived at first breeding both times, and there was approximately 1 year between breedings. Both pregnancies were unremarkable. The first (control) litter, which did not receive LGG, included 7 puppies. The second (LGG) litter, which had been exposed to LGG indirectly through the bitch and directly after birth, included 9 puppies. No adverse effects were evident after administration of LGG to the bitch or the puppies.

Clinical signs and CADESI scores after allergen challenge—In both litters, after the first 2 months of sensitization to the *D farinae* allergen, papules and pruritus were evident on the body sites upon which the allergen was applied. At the end of the sensitization period in the control litter, 7 of 7 puppies developed severe clinical signs of AD after environmental challenge with the allergen. These signs included erythema and pruritus on antebrachial surfaces, pinnae, interdigital spaces, and inguinal areas as well as a fine papular eruption particularly visible on the inguinal area. Signs of severe pruritus (self-trauma and excoriation) were evident in all puppies. In the LGG litter, at the end of the sensitization period, 6 of 9 puppies developed pruritic dermatitis.

When the mean CADESI scores of both litters were compared by use of ANOVA, a significant ($P < 0.001$) main effect of time was detected. Unpaired *t* tests at each time point revealed a significant ($P = 0.005$) difference between CADESI scores for the 2 litters only at 54 hours after the allergen challenge began (Figure 1).

Serologic evaluation—In the control litter, at 6 months of age, 7 of 7 puppies were seropositive for IgE against the allergen *D farinae* and 5 had a titer $\geq 1,500$. The serum titer of allergen-specific IgE in the control litter appeared to increase with age (Figure 2). In the LGG litter, 7 of 9 puppies were seropositive for IgE against *D farinae*, and only 1 dog had a titer $> 1,500$. Serum titers of IgE against *D farinae* in the LGG litter appeared to decrease near the end of the study. When mean titers of allergen-specific IgE were compared between the 2 litters, results of the ANOVA indicated significant main effects of litter ($P < 0.02$) and age ($P < 0.001$) as well as a significant ($P < 0.001$) interac-

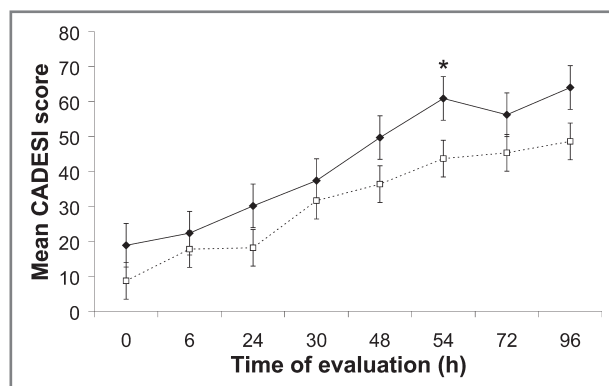


Figure 1—Mean $\pm$ SEM CADESI scores of 2 litters of puppies with experimentally induced AD that were not (diamonds [first litter]; $n = 7$) or were (squares [second litter]; 9) treated with LGG (5 capsules/d [approx 100×10^9 CFUs/d] from 3 weeks of age to 6 months of age). Litters were born of the same bitch, 1 year apart. At 6 months of age, puppies in both litters were environmentally exposed to *Dermatophagoides farinae* for 3 consecutive days, and clinical signs of AD were assessed. *Values differ significantly ($P = 0.005$) between litters at indicated time.

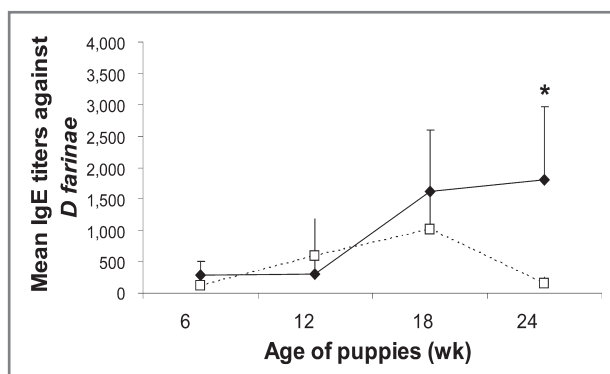


Figure 2—Mean $\pm$ SEM serum titers of IgE against *D farinae* in 2 litters of puppies with experimentally induced AD that were not (diamonds [first litter]; $n = 7$) or were (squares [second litter]; 9) treated with LGG (5 capsules/d [approx 100×10^9 CFUs/d] from 3 weeks of age to 6 months of age). Serum titers in both litters were evaluated when puppies were 6 to 24 weeks of age. *Values differ significantly ($P < 0.001$) between litters at indicated age.

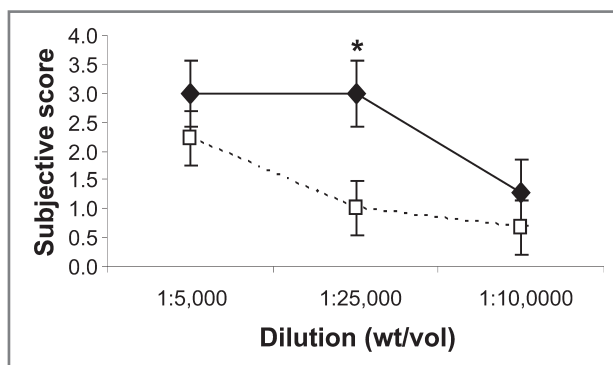


Figure 3—Mean $\pm$ SEM scores for results of skin reactions to intradermal injection of *D farinae* at various dilutions in 2 litters of puppies with experimentally induced AD that were not (diamonds [first litter]; $n = 7$) or were (squares [second litter]; $n = 9$) treated with LGG (5 capsules/d [approx 100×10^9 CFUs/d] from 3 weeks of age to 6 months of age). *Values at indicated dilution were significantly ($P < 0.001$) different between litters.

tion between litter and age. Results of unpaired t tests at each time point suggested that the LGG litter had significantly ($P < 0.001$) lower serum titers of allergen-specific IgE when puppies were 24 weeks of age. There was no significant correlation between serum titers of allergen-specific IgE and mean or maximum CADESI scores in either litter.

Intradermal allergen test scores—In the control litter, 6 of 7 puppies had a positive reaction to the intradermal allergen test, indicating they had been sensitized to *D farinae*. In the LGG litter, 3 of 9 puppies had a positive reaction. Results of the ANOVA indicated a significant effect of litter ($P = 0.02$) and concentration ($P = 0.001$) as well as a significant ($P = 0.03$) interaction between the 2 variables. Additionally, results of an unpaired t test suggested a significantly ($P < 0.001$) different degree of reactivity to the intradermally administered allergen at 1:25,000 (wt/vol) in the LGG litter, compared with the degree of reactivity in the control litter (Figure 3).

Discussion

The present study revealed that administration of LGG to puppies was associated with a reduced mean serum titer of IgE against *D farinae* and reduced skin reactivity to intradermal injection of that allergen, compared with respective values for puppies that did not receive LGG. However, LGG administration did not appear to reduce the clinical signs of AD.

The decrease in the serum titer of allergen-specific IgE was in agreement with results of studies^{29,30} involving humans, in which a decrease in allergen sensitization was detected when women with AD or eczema ingested probiotics during gestation and lactation. Other studies^{31,32} revealed no change in serum titers of allergen-specific IgE when infants with AD began treatment with probiotics after birth. Therefore, it appears that age of administration has an important influence on serum titers of allergen-specific IgE. The decrease in serum titers of allergen-specific IgE in rodents has also been reported.^{17,33,34} In the present study, blood samples were

not obtained from the bitch at multiple points to determine the effect of LGG administration on the serum titer of allergen-specific IgE in that dog. Consequently, it is unknown whether a decrease in serum titer of allergen-specific IgE can be obtained in adult dogs.

The clinical effect of probiotic treatment on clinical signs of AD is a topic of controversy. In the present study, no significant decrease in clinical signs was detected in puppies treated with LGG. In another study³⁵ involving mice, suppression of the clinical signs of dermatitis took place when probiotics were administered early in life. On the other hand, a systematic review³⁶ of the benefits of probiotic administration in children with various hypersensitivities yielded inconclusive results. Evidence in human medicine suggests that probiotics are more effective in the prevention of AD rather than treatment of established AD.³⁷

In the study reported here, a probiotic developed for treatment of humans was used. This probiotic was selected for various reasons, including the results of other studies that suggested LGG may be useful for treating dogs,^{22,38} the apparent lack of adverse effects such as promotion of adhesion of microbial pathogens to the jejunum,³⁹ the reliability of the commercial product containing LGG,^{40,41} and the establishment of a dose sufficient to colonize the gastrointestinal tract of dogs.²² Furthermore, the ability of lactic acid bacterial species to adhere to intestinal mucus does not appear to be host specific but, rather, appears to be a characteristic of the bacterial species.⁴² A potential disadvantage of LGG for treatment of dogs is the large dose necessary to achieve a purported effect.²² Administration of 10 capsules/d costs approximately \$8/d, and some clients and dog breeders may consider this cost prohibitive.

The present study had several limitations that need to be considered when interpreting the results. The number of dogs evaluated was small, and as a consequence, large variability existed among dogs, thereby reducing the power to detect a significant difference between litters. Another important consideration is that an experimental model of AD was used in this study. The puppies used were highly predisposed to AD and had severe clinical signs of disease. It is not known whether the AD in the study dogs was fully representative of naturally developing AD; therefore, it is not known whether the same results would be detected in client-owned dogs with AD. One must also consider that the investigator evaluating the dogs was aware of the treatment each litter received. However, records of results for the first litter were not accessed by the investigator between litters, and recollection of those results diminished by the time the study concluded, helping to reduce that potential source of bias. In addition, an independent laboratory⁸ processed the serum samples for serologic testing for titers against allergen-specific IgE, and this laboratory was unaware of treatments received. Because of technical constraints, the investigator was precluded from evaluating the effect of LGG treatment on the intestinal flora of dogs.

In the study reported here, administration of LGG did not prevent the development of AD in a third of the puppies treated with the probiotic; therefore, no claims can be made with regard to its clinical benefits. There

was evidence that administration of LGG did alter the immune response as reflected by lower scores for intradermal allergen reactions and lower titers of allergen-specific IgE in puppies treated with LGG, compared with respective values in control puppies. However, larger studies in nonexperimental settings are needed to determine whether treatment with LGG does or does not have an effect on clinical signs of AD in affected dogs.

- a. Allercept, Heska Corp, Fort Collins, Colo.
- b. RMB83M, Greer Laboratories Inc, Lenoir, NC.
- c. Science Diet Canine Adult Maintenance, Hill's Pet Nutrition, Topeka, Kan.
- d. Science Diet Puppy Healthy Development Savory Chicken Entrée dog food, Hill's Pet Nutrition, Topeka, Kan.
- e. MITE-T-Fast Allergen Detection System, Aveho Biosciences, Monterey, Tenn.
- f. Culturelle HS, Amerifit Brands/Culturelle, Cromwell, Conn.
- g. Heska Corp, Fort Collins, Colo.
- h. JMP, SAS Institute Inc, Cary, NC.

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Correction: Experimental primary ocular canine herpesvirus-1 infection in adult dogs

Figure 3 in the report “Experimental primary ocular canine herpesvirus-1 infection in adult dogs” (*Am J Vet Res* 2009;70:513–521) is incorrect. The correct figure and legend are as follows.

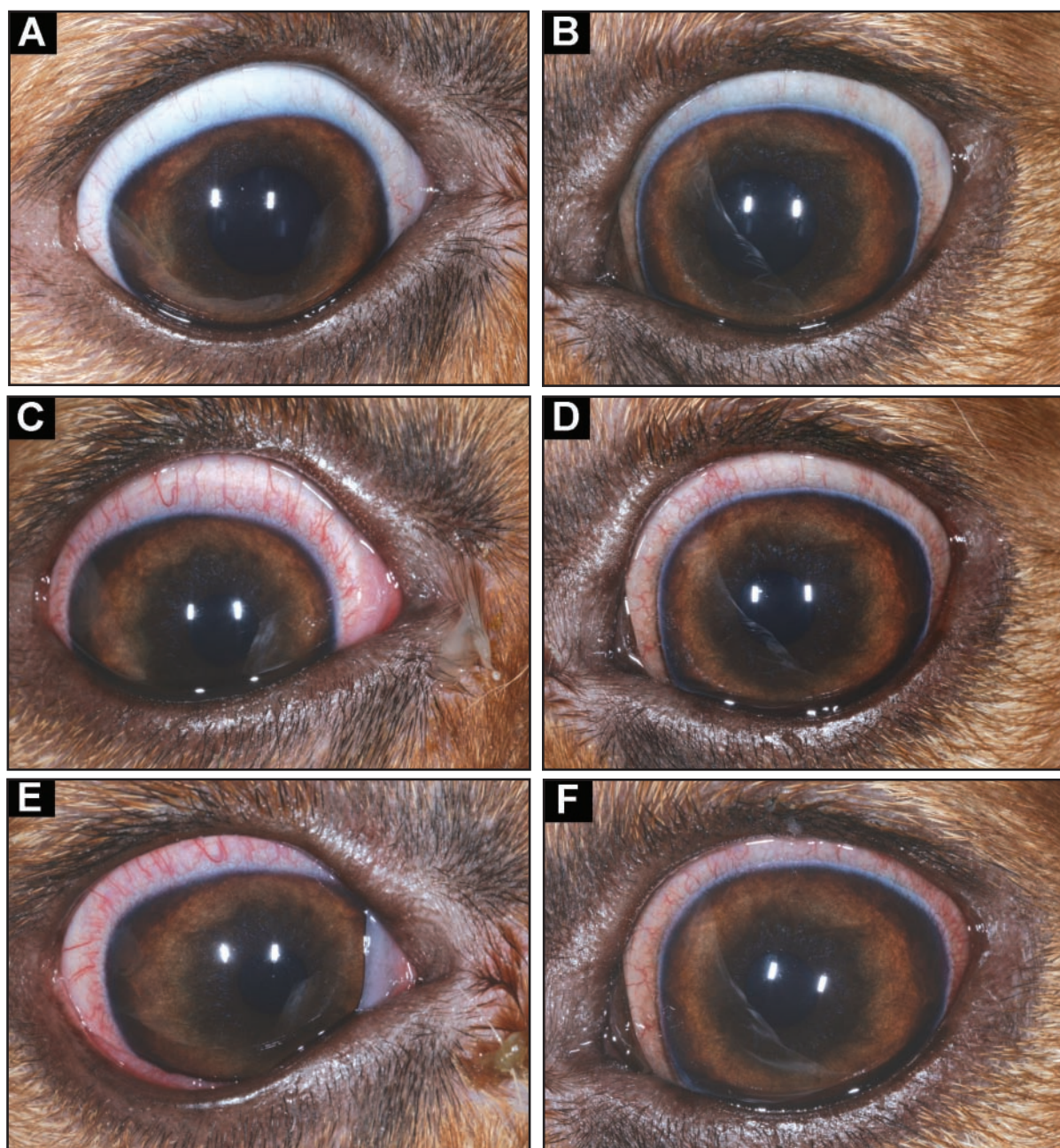


Figure 3—Photographic views of the inoculated (A, C, E) and noninoculated (B, D, F) eyes of 1 adult dog with experimentally induced primary ocular CHV-1 infection. A, B = Prior to infection. C, D = PID 5. E = PID 7. F = PID 10.