

Evaluation of a commercial staphylococcal bacterin for management of idiopathic recurrent superficial pyoderma in dogs

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SUMMARY

Twenty-one dogs with idiopathic superficial recurrent pyoderma were entered into a double-blind, placebo-controlled study to evaluate the efficacy of a commercial staphylococcal bacterin. The study spanned an 18-week period. All dogs were administered sodium oxacillin orally for the initial 6 weeks of the study. Dogs were given the bacterin or placebo SC, twice weekly at 3- or 4-day intervals, beginning at week 0 and continuing for 18 weeks. Dogs given antibiotics plus the bacterin ($n = 13$) had a significantly ($P < 0.05$) better treatment response than those given antibiotic plus placebo.

Recurrent staphylococcal skin infection (pyoderma) is a canine skin disease seen frequently in veterinary practice. The disease can be difficult to manage and frustrating for owners. Typically, an affected dog develops superficial or deep pyoderma that responds to oral administration of appropriate antibiotics, but recurs within a few weeks after cessation of antibiotic treatment. Veterinarians first seek an underlying systemic disorder (eg, hypothyroidism, allergic disease, occult neoplasia, or other organ failure) that would explain the recurrence. When exhaustive diagnostic evaluation fails to reveal an underlying cause, dogs must often be given antibiotic treatment indefinitely to prevent recurrence. Constant antibiotic administration represents a financial burden to the owner and frustration for the veterinarian, and could promote development of antibiotic-resistant strains of *Staphylococcus* bacteria.

Staphylococcal bacterin preparations are reported to be efficacious as adjunct treatment in management of some canine pyogenic skin infections.¹⁻³ The purpose of the double-blind, placebo-controlled study reported here was to document the efficacy of a commercial staphylococcal bacterin in the management of idiopathic recurrent superficial pyoderma in dogs.

Materials and Methods

Patient selection and initial evaluation—Dogs were selected from the patient population at the university veterinary medical teaching hospital. Each dog had a well-documented history of recurrent superficial pyoderma for which underlying cause could not be determined. All dogs entered into the study ($n = 21$) had a history of complete response of their skin disease to antibiotic administration (ie, return to clinical normalcy), followed by relapse when antibiotics were discontinued. Other nonantibiotic treatments, such as frequent shampooing with antibacterial shampoos, had failed to prevent relapse in all affected dogs. Minimal diagnostic evaluation of dogs prior to selection for the study consisted of a CBC, serum biochemical analysis, measurement of baseline serum thyroxine (T_4) and triiodothyronine (T_3) concentrations, examination of skin scrapings for ectoparasites, fungal culture, and intradermal skin testing for inhalant allergy. All dogs were undergoing a relapse of pyoderma at the time of admission to the study.

Thorough physical examination was performed on each dog at the time of entry into the study. Detailed history was obtained, and photographs were taken of lesional areas. A pustular lesion was pricked open, using a sterile needle, and was swabbed, using a sterile cotton swab. The swab specimen was submitted for bacteriologic culture and identification, biotyping,^a and antimicrobial susceptibility testing of bacterial growth.

Study protocol—The study was conducted between February and December 1987. Treatment spanned an 18-week period, with reevaluation performed at weeks 6, 10, 14, and 18 (Fig 1). All dogs were administered sodium oxacillin (20 mg/kg of body weight, PO, q 8 h), for the initial 6 weeks of the study. Benzoyl peroxide shampoo (2%)^b was used on all dogs once to twice weekly, during the entire study, to kill staphylococci topically.^c Concurrent with antibiotic treatment, dogs were given either a commercial staphylococcal bacterin (*Staphylococcus* phage lysate-SPL^d) or placebo (beef heart infusion broth, the vehicle for the commercial bacterin) in blinded fashion. Assignment to either the SPL group or the placebo group was random. Vials were identified by a code number and were identical in appearance so that neither the owner nor the study personnel knew which substance was administered. The dosage regimen for SPL or placebo injections was as follows: starting the first week of the study, each dog was given 0.5 ml of SPL or placebo SC twice weekly, at 3- to 4-day intervals. The SPL or placebo was administered at home by the owner, after instruction. Injections were

^a Staph-Ident system, API Analytab Products, Plainview, NY.

^b OxyDex shampoo, Dermatologics for Veterinary Medicine, Miami, Fla.

^c Kwochka KW, Kowalski JJ. In vivo effect of four commercial antimicrobial shampoos against *Staphylococcus intermedius* in the dog (abstr), in *Proceedings, Annu Meet Am Acad Vet Dermatol* 1989;65.

^d Staphage lysate, Delmont Laboratories, Swarthmore, Pa.

Received for publication Oct 25, 1988.

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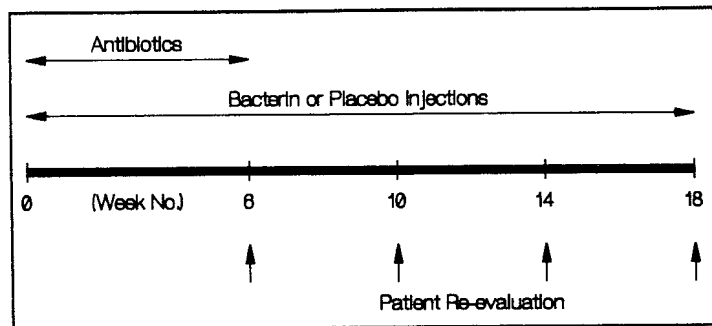


Fig 1—Time schedule for the study. All dogs were given antibiotics for the first 6 weeks. Dogs also were given bacterin or placebo injections twice weekly, starting at week 0, during the entire study. Arrows indicate time points for clinical reevaluation of dogs.

TABLE 1—Clinical evaluation scores* for dogs of the study

Grade	Recurrence seen	Control evident	Antibiotics needed†
1	None	Yes	No
2	Mild	Yes	No
3	Mild	Yes	Yes
4	Mild to moderate	No	Yes
5	Severe	No	Yes
6‡	Worse than ever	No	Yes

* The scores were assigned based on extent of recurrence, whether some degree of control was evident in response to the injection, and necessity of prescribing additional antibiotic treatment to keep the dog comfortable.

† If antibiotics were needed for patient comfort, oxacillin was reinstated at the prior dose for 2 weeks only.

‡ For grade 6, the disease was more severe than before, as if it were made worse by the injections.

continued during the initial 6-week course of antibiotic treatment and for 3 months after cessation of antibiotics (18 weeks total).

Evaluation during study—Each dog was evaluated at the end of antibiotic administration (6 weeks after the start of the study) and monthly thereafter for 3 months (Fig 1). Two veterinarians performed the examinations and evaluated response of the disease. Each dog was evaluated by both veterinarians by the end of the study; no dog was examined by the same veterinarian at all visits. At reevaluation visits, each dog was assessed clinically for the presence and extent of pyoderma, a specimen for bacteriologic culture and antimicrobial susceptibility was obtained if needed (clinical score, ≥ 3), and photographs were taken. Owners were questioned to determine whether signs of recurring pyoderma had been noticed and severity of such signs. At each visit, the examiner assigned a clinical score to the dog based on predetermined criteria (Table 1). At the conclusion of the 18-week study, the blind code was broken to determine to which group the dog had been assigned.

Statistical analysis—Scores for all dogs were tabulated by week number and were separated into the group that was given SPL and the placebo group. Differences in treatment effects between the 2 groups were determined at 10, 14, and 18 weeks, using a nonparametric Kruskal-Wallis test modified for analysis of ordinal categorical data.⁴ Treatment response was considered significantly different if P value was < 0.05 .

Results

Twenty-one dogs completed the study; 8 were given placebo injections, and 13 were given SPL. None of the owners reported any adverse reactions to the injections.

TABLE 2—Clinical results of treatment of 21 dogs with placebo or staphylococcal phage lysate (SPL)

Dog No.	Treatment	Clinical evaluation score*			
		10 Wk	14 Wk	18 Wk	Mean
4	Placebo	3	3	3	3.0
5	Placebo	2	2	2	2.0
6	Placebo	2	3	4	3.0
9	Placebo	2	4	4	3.3
10	Placebo	5	5	5	5.0
13	Placebo	1	2	2	1.7
17	Placebo	2	3	3	2.7
	Averages	2.62	3.25	3.38	3.08
1	SPL	1	1	2	1.3
2	SPL	1	2	3	2.0
3	SPL	3	4	4	3.7
7	SPL	3	5	4	4.0
8	SPL	1	1	1	1.0
11	SPL	2	3	3	2.3
12	SPL	3	1	3	2.3
14	SPL	4	6	5	5.0
15	SPL	1	2	2	1.7
16	SPL	2	2	2	2.0
18	SPL	1	1	1	1.0
20	SPL	2	1	1	1.3
21	SPL	1	1	1	1.0
	Averages	1.92†	2.31†	2.46†	2.23

* Clinical evaluation score ranged from 1 to 6, with 1 as the best clinical response (see Table 1 for key). † Indicates significant difference from placebo-treated group; $P < 0.02$ for week 10, $P < 0.05$ for week 14, and $P < 0.01$ for week 18.

Prior to antibiotic treatment, *S intermedium* was isolated in pure culture from lesions from all dogs. All isolates were sensitive to oxacillin as determined by results of the Kirby-Bauer disk method, using a methicillin disk. Repeat culturing ($n = 26$) was performed during the study; all isolates were still *S intermedium* and still sensitive to oxacillin.

At the end of week 6, no dog had evidence of superficial pyoderma and, therefore, all received a score of 1. Scores at the 10-, 14-, and 18-week visits are seen in Table 2; final mean scores for each dog (mean scores for 10-, 14-, and 18-week visits) are also shown. A final mean score < 3.0 (according to the criteria in Table 1, some degree of disease control achieved) was termed good clinical response, and a final mean score ≥ 3.0 (no control achieved or disease made worse) was termed poor response. Using this criterion, 10 of 13 dogs (77%) of the group given SPL had good clinical response (range of scores, 1.0 to 2.3; mean, 1.6). The remainder of SPL-treated dogs (23%) had poor clinical response. In dogs of the placebo group, 3 of 8 (46%) had good clinical response (range of scores, 1.7 to 2.7; mean, 2.1). Of 8 placebo-treated dogs, 5 (63%) had poor response to injections, with final mean scores ranging from 3.0 to 5.0 (mean, 3.7). The overall mean score for SPL-treated dogs was 2.23, and for placebo-treated dogs was 3.08. There was a significant ($P < 0.05$) difference between the SPL- and placebo-treated dogs in terms of clinical improvement and control of recurrent pyoderma at weeks 10, 14, and 18.

Subjectively, owners and investigators observed that dogs that benefitted from SPL treatment sometimes developed pyoderma lesions during periods of remission. However, owners reported that lesions were typically fewer and milder than had been seen previously and resolved spontaneously in a few days. Owners frequently commented that prior to the study, such lesions would have worsened and proliferated rapidly.

Twenty-two months after conclusion of the study, par-

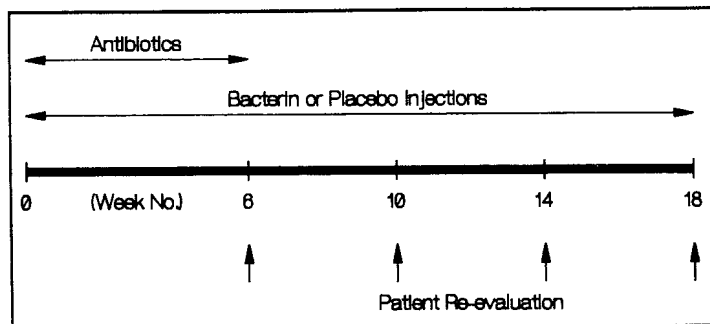


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sensitivity in dogs based on histologic criteria and intradermal skin test reactions. Preliminary reports by one investigator indicate that dogs with recurrent pyoderma have high serum concentrations of antistaphylococcal IgG and IgE.²⁴

Staphylococcal phage lysate has a variety of effects on the immune response that may have clinical relevance. It must be emphasized that some of these effects have marked species variation; therefore, any speculation as to mechanisms of action of SPL should include consideration of the species being studied. Effects of SPL include antigen-specific and nonspecific phenomena, and involve cellular and humoral immune responses. Augmentation of the primary antibody response to specific antigen has been observed in mice in response to injection of SPL, as well as nonspecific increases in serum IgG concentration in this species.¹⁰ Staphylococcal phage lysate induces lymphocyte blastogenesis in T, B, and null lymphocytes in human beings and rabbits, but not in mice or rats.^{5,26} It also induces production of interferon and lymphokines in human lymphocytes.²⁷ In mice, the lymphokines have the ability to inhibit macrophage migration and increase phagocytosis of bacteria by macrophages.²⁸ Thus, SPL has had a variety of effects on the immune response in experimental studies; which of these effects, if any, are important in clinical efficacy is not known.

It is probable that repeated injection of SPL in dogs induces specific humoral and cellular immune responses directed against *S aureus* antigens. Because there is considerable antigenic cross-reactivity between *Staphylococcus* strains,²⁹ some of these antigens are likely present in pathogenic *S intermedius* strains that cause canine pyoderma. Thus, there are additional mechanisms by which SPL may exert beneficial actions in dogs with this disease, other than by the nonspecific effects discussed previously. For example, SPL could be augmenting the host defense against staphylococci by increasing specific antistaphylococcal antibody titer, or by enhancing cellular immune responsiveness to the bacteria. Alternatively, if immediate hypersensitivity to bacterial antigens is part of the pathogenesis of recurrent pyoderma, SPL could be acting to hyposensitize the individual against these antigens.

In conclusion, results of this study indicated that SPL can be an effective adjunctive treatment in management of idiopathic recurrent superficial pyoderma in dogs. Because SPL is a product containing a variety of substances with a variety of actions, further investigation into which components provide therapeutic benefit and which immunomodulatory actions are important in dogs may help define the pathogenesis of recurrent pyoderma and lead to development of even more efficacious immunomodulatory agents.

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