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Reduced antimicrobial prescribing during autogenous staphylococcal bacterin therapy: A retrospective study in dogs with pyoderma

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ABSTRACT

Autogenous staphylococcal bacterins are commonly mentioned as treatment for canine recurrent pyoderma but little evidence is known about their efficacy. This retrospective study describes use and assesses efficacy of an autogenous *Staphylococcus (pseud)intermedius* bacterin in dogs with pyoderma. Frequency and duration of systemic antimicrobial therapy were compared 12 months before and after starting bacterin (Wilcoxon-signed-rank test) with data extracted from general practice medical histories.

Bacterin orders had been received by the laboratory for 231 dogs over a 12.5-year period. Complete medical records could be obtained for 22 dogs. All had received at least one course (median 5, range 1-10) of systemic antimicrobials before starting bacterin. After starting bacterin, five dogs (22.7%) did not receive any antimicrobials systemically; 17 (77.3%) received fewer courses and days compared to the preceding 12 months (P=0.007 for both courses and days). No bacterin-associated adverse effects had been recorded.

Although primary causes for pyoderma and the effect of topical therapy were not controlled in this study, the data provide additional evidence of a beneficial effect of autogenous *S. pseudintermedius* bacterin in the management of canine recurrent pyoderma. Autogenous bacterin therapy should be studied further as an aid to treatment in the context of good antimicrobial stewardship.

INTRODUCTION

With antimicrobial resistance as a major threat to human and animal health, veterinary prescribing of antimicrobial drugs is under scrutiny, for both livestock and for companion animals. Canine pyoderma remains one of the most common diseases diagnosed in small animal practice,[1 2] frequently leads to antimicrobial prescribing[3] and is often recurrent due to undiagnosed or uncontrolled underlying primary triggers.[4-7]

Repeated systemic antibacterial treatment is discouraged in order to reduce resistance selection pressure on skin microflora and skin pathogens.[8] However, other management options for recurrent pyoderma are scarce, with topical antibacterial therapy as an attractive, but not always practical, alternative.[9-11] Immunomodulation or immunisation through staphylococcal vaccines have been explored for many decades, mainly for application in bovine mastitis and in human furunculosis and rhinitis.[12-15] In human medicine, several vaccine candidates, targeting different antigens, have progressed through to clinical trials but efficacy against invasive *S. aureus* infections in clinical phase III stages have so far been disappointing.[16 17]

Bacterins, defined as suspensions typically of lysed or attenuated bacteria used as vaccines to increase immunity to particular pathogens or a disease, have been used sporadically in dogs for staphylococcal blepharitis[18] and for recurrent staphylococcal pyoderma.[19-24] Clinical benefits have been reported but associated immunological changes remain rarely studied[25] and poorly understood.

Two early bacterin studies published in the 1980s already indicated a beneficial effect as adjunctive therapy in the management of superficial and deep canine pyoderma. One was a *Propionibacterium acnes* (now referred to as *Cutibacterium acnes*)[26] suspension,[19] the other an autogenous '*S. aureus'* lysate (possibly *S. pseudintermedius* in current taxonomy).[20] However, the intravenous injection route for the *P. acnes* product and the high incidence of local and systemic adverse reactions with the *S. aureus* bacterin limited practical clinical utility.

Later, two controlled studies assessed the efficacy of bacterins specifically in dogs with superficial pyoderma. Staphage Lysate (SPL, Delmont Laboratories, Swarthmore, PA, U.S.A.), a phage lysate of well-characterised *S. aureus* cultures, commercially available in the U.S.A. and selected other countries, was tested in 21 dogs with superficial pyoderma against placebo in a double-blinded design with twice weekly subcutaneous injections over 18 weeks and once or twice weekly washing with a benzoyl peroxide shampoo for both groups.[21] A beneficial effect was seen in 77% of dogs in the treatment group with regard to milder or less frequent recurrence of pyoderma or reduced need of antimicrobials compared to 37% improvement in the placebo group. Efficacy was also reported for an autogenous *S. (pseud)intermedius* bacterin formulated through phenol and formalin processing of the patient's own pathogenic staphylococcal isolate.[22] After a ten-week, single-blinded treatment period, lesion scores in the five control group dogs were significantly higher than those in the five dogs receiving subcutaneous bacterin injections. In both studies, systemic antibiotics were given initially in parallel to bacterin therapy for six and four weeks respectively, reflecting the concept of bacterins as an aid to prevent recurrences rather than a treatment for active infection. Lastly, two uncontrolled studies reported beneficial effects on clinical signs in dogs with recurrent pyoderma. The SPL reduced pruritus scores in 13 atopic dogs[23] and another *S. aureus* lysate, originally developed for use in bovine mastitis (Lysigin, Boehringer Ingelheim Vetmedica, Inc. St. Joseph, MO, U.S.A.) reportedly improved pyoderma

lesions in all ten dogs with superficial pyoderma and in nine of eleven dogs with deep pyoderma over a four-month period of subcutaneous injections.[24]

Our retrospective study aimed to describe how the autogenous *S. (pseud)intermedius* bacterin previously investigated by Curtis *et al*.[22] is used in veterinary practice and to assess whether it could reduce the need for systemic antimicrobial therapy in dogs with recurrent pyoderma.

MATERIALS AND METHODS

Ethics

The study had been approved by the Royal Veterinary College (RVC) Ethics and Welfare Committee (URN 2014 1294).

Bacterin orders and treatment recommendations

Information on autogenous *Staphylococcus (pseud)intermedius* bacterins ordered for dogs from the RVC microbiology laboratory between January 2002 and June 2014 was reviewed. Bacterins had been formulated as previously described (production discontinued since 2018) from clinical isolates of *S. pseudintermedius* (*S. intermedius* prior to 2009) through processing with phenol and formalin.[22] Bacteria had been isolated from clinical samples submitted by veterinary surgeons (first opinion veterinarians and referral veterinary dermatologists) for bacterial culture, antimicrobial susceptibility testing and bacterin production, or isolates had been submitted for bacterin formulation via another diagnostic laboratory on behalf of the submitting veterinary surgeon.

Bacterins were posted to submitting practices with instructions for subcutaneous administration (Table 1). Antimicrobial treatment before and during the start of bacterin therapy was at the veterinary surgeon's discretion but discontinuation approximately ten days into bacterin treatment was recommended. Numbers of first orders, of subsequent repeat orders and intervals between first orders and first and last repeat orders were recorded. Based on volume (40ml per vial) and recommended injection protocol, one vial was assumed to provide 81 days of induction course treatment and between 91 and 192 days of maintenance treatment at either weekly or fortnightly dosing. Orders submitted after more than 192 days were included as new orders.

Antimicrobial use and clinical characteristics

Antimicrobial use before and during bacterin therapy, including treatment during the start of bacterin injections, was investigated by retrospective analysis of the dogs' medical records. Practices in the U.K. that had ordered bacterin for a dog with a methicillin-susceptible *S. (pseud)intermedius* and for which addresses could still be obtained from the RVC laboratory database were asked in writing to send patient medical histories covering 12 months before and 12 months after starting bacterin therapy. Practices were asked to submit medical records coded with the study number provided on the covering letter and with all owner identifiable data deleted. Medical histories were not requested if bacterins had been ordered through another microbiology laboratory on behalf of the attending veterinary surgeon. One follow-up phone call was made two to four weeks after the initial request if histories had not been received.

Medical histories were analysed for signalment (recorded as close as possible to the start of bacterin therapy), diagnosis of skin disease (as recorded by submitting practices or as

predicted from descriptions of lesion type), timing and duration of bacterin injections and for systemic (days of drug prescribed for bacterial infections) and topical (prescribed or not) antibacterial therapy. Pyoderma was classified based on clinical signs into superficial (papules, pustules, epidermal collarettes) or deep (furuncles, sinuses, haemorrhagic crusts). Records of adverse reactions in a timely association with bacterin injections were noted.

Statistical Analysis

Data were described and analysed using SPSS Version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY). Distribution of data was tested for normality using the Shapiro-Wilk test. Differences between numbers of days and numbers of courses of antimicrobial drugs prescribed for systemic use were compared before and during bacterin therapy for each dog by Wilcoxon signed rank test. $P<0.05$ was considered statistically significant.

RESULTS

Bacterin orders

Totals of 231 new *S. (pseud)intermedius* bacterin requests (mean 18 per year, SD 6.7) and of 480 repeat orders (mean 38 per year, SD 12.2) were received by the RVC laboratory during the twelve-and-a-half-year study period. Of the 231 dogs for which bacterin had been ordered, 137 (59.3%) continued with at least one repeat order. The number of repeat orders per individual dog ranged from 1 to 16 (median 3) with repeats ordered only once for 47 (20.3%) dogs, twice for 19 (8.2%) dogs and more than twice for 71 (30.7%) dogs. Orders for first repeat bacterin vials were received within 13 weeks of the first order for 68 (50%) dogs, in compliance with the expected ordering interval according to the dosing protocol. Of 305 ordering intervals available for consecutive repeat orders, 75.1% were within the appropriate predicted treatment duration.

Clinical characteristics of bacterin-treated dogs

Medical histories were requested for 144 of the 231 dogs from 47 different primary practices. Medical records were not requested for the remainder as dogs either lived outside the U.K. (n=12, all in Germany), bacterin had been ordered through another U.K. diagnostic laboratory (n=39), addresses for submitting practices were no longer valid (n=31) or medical records for the relevant period could not be accessed conveniently after practices had changed from paper to computer records (n=5).

Records were returned for 45 of the 144 dogs (31.3% response rate) with information covering the required 24-month period for 22 dogs (signalment in Table 2). In addition to their pyoderma management, eleven dogs (50%) received ectoparasite prophylaxis prescribed by their veterinary surgeons during their study periods. Allergic skin disease was recorded as diagnosed or suspected based on clinical signs in 17 (77.3%) dogs. Eleven of those (64.7%) received concurrent treatment with a systemic glucocorticoid (10 dogs) or ciclosporin (1 dog) for management of underlying allergic disease; there was no difference between the number of dogs responding or not responding to bacterin (antimicrobial courses reduced or not) between allergic patients receiving systemic anti-inflammatory treatment and those that did not ($P=0.65$ and $P=0.98$, 2-tailed Fishers exact for antimicrobial courses and days respectively). Other chronic diseases mentioned were

hypothyroidism in two dogs, a keratinisation disorder in one and heart disease in another three dogs, all managed with systemic or topical medication in parallel to their pyoderma.

No adverse effects (at injection sites, or to general health) had been recorded in a timely relation to bacterin therapy in any of the dogs.

Antimicrobial use before and during bacterin therapy

In the 12 months before starting bacterin therapy, all 22 dogs had received at least one course or a minimum of 14 days of systemic antimicrobials (Table 2). In the 12 months after starting bacterin therapy, five dogs (23%), four with superficial and one with deep pyoderma, had not received any systemically used antimicrobials. Fewer courses and fewer days of systemic antimicrobial therapy had been prescribed during the 12 months following the start of bacterin therapy compared to the 12 months preceding bacterin ($P=0.007$ for both courses and days comparing all 22 dogs). Ranges and medians are shown in Table 2. When only comparing the 19 dogs for which at least one repeat bacterin order had been received and which had therefore likely received at least 172 days of bacterin therapy, antimicrobial prescribing before and after bacterin start was also reduced for courses and days (both $P=0.02$).

Six different classes of systemic antimicrobial drugs had been prescribed for the 22 dogs. All but one had received a β-lactam antibiotic on at least one occasion during their 24-month study period (cephalexin prescribed for 20 dogs, amoxicillin-clavulanic acid for 13 dogs, cefovecin for 4 dogs on at least one occasion), clindamycin had been used in 5 dogs, a fluoroquinolone in 7, and 1 dog had been treated with trimethoprim-potentiated sulphonamide. Topical antimicrobial therapy had been dispensed in addition to systemic treatment in 15/22 (68%) dogs during the 24-month periods but prescriptions were too infrequent to allow useful allocation into periods before and after starting bacterins. Prescription-only, chlorhexidine-based shampoos (Malaseb, Dechra Veterinary Products, Shrewsbury, U.K.; Microbex, Virbac Limited, Woolpit, U.K.) indicated for the management of microbial skin infections had been used for 8/22 (36%) dogs, another six dogs had received other antibacterial wash preparations (chlorhexidine, hypochloric acid or chloroxylenol-based products) and one dog had received fusidic acid cream as the only topical product. Of the five dogs that had been managed without systemic antimicrobials after starting bacterin, three continued with antimicrobial shampoo therapy. Antimicrobial eardrops had been prescribed for 10/22 dogs at least once during the 24 months periods.

DISCUSSION

Within the limitations of a retrospective study using general practice medical records, our results suggest that autogenous *S. (pseud)intermedius* bacterin can help to reduce the need for systemic antimicrobial therapy in the management of canine recurrent pyoderma. For the first time in canine pyoderma, this study analysed the need for antimicrobial medication during bacterin therapy over a long period, rather than clinical signs during shorter trials as in previous studies. The reduced need for antimicrobial therapy is in line with findings from a recent study in pigs where an autogenous *S. hyicus* vaccine used in sows reduced the metaphylactic use of antimicrobials in their piglets during outbreaks of exudative epidermitis but where management and other concurrent factors were well controlled.[27] Reducing the need for systemic antimicrobials in dogs is of particular

relevance at a time when calls to reduce antimicrobial use in companion animals, and in some countries restrictions on prescribing, are increasing.[28-30]

Acceptance of the bacterin therapy amongst owners and veterinary surgeons and safety in the dogs appeared good based on repeat orders received for almost 60% of dogs after the initial 80-day course and the lack of any mention of adverse reactions in the medical records of the 22 dogs.

Important confounding factors in this study were the lack of standardisation or control of diagnostic criteria and of primary causes for pyoderma. Diagnostic detail such as the level of depth for pyoderma (superficial or deep) was recorded but diagnostic criteria had not been determined prospectively. Although in one study, bacterin therapy was less effective in dogs with deep pyoderma compared to those with superficial infections,[24] unfortunately, this layer of analysis could not be included in this study. Furthermore, critical steps towards successful management of recurrent canine pyoderma remain the investigation and correction of primary diseases that lead to bacterial skin infection, most commonly ectoparasite infestations and allergic skin disease.[7 31] Unfortunately, diagnostic investigations into such primary skin diseases seem rarely exhaustive in small animal practice as highlighted by a recent observational study that found that definitive diagnoses were only rarely reached before management decisions were made.[32] Similarly, the results from our study indicate that ectoparasite prophylaxis, topical antimicrobial therapy and anti-inflammatory medication for dogs with allergic skin disease were probably underused with only 50% of dogs receiving veterinary-prescribed ectoparasite control and only 50% of allergic dogs receiving anti-inflammatory medication for their allergic skin disease.

In current clinical practice, a major challenge to the treatment of canine pyoderma is the increasing prevalence of multidrug-resistant, methicillin-resistant *S. pseudintermedius* (MRSP).[10] Autogenous bacterins may be of value in reducing selection pressure on opportunistic staphylococci by reducing the need for repeated systemic antimicrobial therapy and thus the risk of selection for MRSP. However, bacterin therapy has not been shown to speed up resolution of clinical signs, which should be the primary focus in the management of any MRSP infection in order to reduce the risk of contagion and zoonotic transmission. Furthermore, it remains unknown whether individual resistance genes are destroyed during bacterin production. Until this has been resolved, bacterins should only be prepared from methicillin-susceptible *S. pseudintermedius* to avoid the potential dispersal of resistance genes.

In summary, the results from this study corroborate findings from the six earlier studies on canine recurrent pyoderma[19-24] and expand the conclusions of a recent review that staphylococcal bacterin therapy can be of value in the management of canine recurrent pyoderma.[33] Further investigations to better understand underlying mechanisms and optimise treatment are clearly needed. Such efforts would now be timely and relevant due to the high level of morbidity associated with canine recurrent pyoderma and the public health implications of repeated use of systemic antimicrobials that are classified as critically important for human health by the World Health Organisation.[34]

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Table captions

Table 1: Protocol and treatment recommendations provided to veterinary surgeons with each RVC *Staphylococcus* autogenous bacterin vial for injecting dogs.

Table 2: Characteristics and antimicrobial therapy in the 12 months before and after starting autogenous *Staphylococcus (pseud)intermedius* bacterin for bacterial skin infections in 22 dogs**.**

Table 1: Protocol and treatment recommendations provided to veterinary surgeons with each RVC *Staphylococcus* autogenous bacterin vial for injecting dogs

Recommendations	Treatment protocol	
Before starting induction bacterin therapy and during initial ten-day period	Antibiotics should be withdrawn approximately 10 days after the injections begin, assuming that pyoderma is controlled. Once opened, please keep the bacterin refrigerated and inject subcutaneously every 3-4 days as follows:	
	Day 1	1 ml
	Day 4	1 ml
	Day 8	2 ml
	Day 11	2 ml
	Day 15	3 ml
	Day 18	3 ml
Subsequent induction therapy and maintenance	Continue with 3 ml dose on a weekly basis.	
Continuation therapy	If after three months the animal is responding favourably, then the injection interval can be extended to ten days and gradually to two weeks.	

Table 2: Case characteristics and antimicrobial therapy before and after starting autogenous *Staphylococcus (pseud)intermedius* bacterin for bacterial skin infections in 22 dogs

Dog number	Breed	Sex	Body weight (kg)	Age (years)	Type of pyoderma as recorded in medical records	Number of repeat orders	Systemic antimicrobial therapy			
							Courses before	Courses after	Days before	Days after
1	Unknown	Not known	28	Not known	Deep interdigital	4	4	2	37	7
2	Dalmatian	F	30	6.5	Superficial and interdigital	3	11	7	81	77
3	Cairn terrier	M	13	7	Deep interdigital	3	3	4	27	77
4	Shar Pei	M	20	1.5	Superficial pyoderma	4	4	0	32	0
5	Italian Spinone	F	30	5.5	Superficial pyoderma	1	1	0	14	0
6	Doberman	M	39	2.2	Superficial and deep	11	6	2	96	27
7	Bullterrier	F	24	4.5	Deep pyoderma	12	6	5	237	65
8	German shepherd	F	29	5.4	Superficial pyoderma	4	3	8	76	77
9	Yorkshire terrier	F	4.5	11	Superficial pyoderma	2	9	6	190	196
10	Yorkshire terrier	F	4	10	Superficial pyoderma	3	6	2	116	27
11	Cavalier King Charles spaniel	M	12.5	8	Superficial pyoderma	1	3	6	59	46
12	Labrador retriever	M	35	6	Superficial pyoderma	1	6	3	43	65
13	Labrador retriever	M	32	6	Superficial pyoderma	1	6	5	65	133
14	Rhodesian Ridgeback	F	52	2	Superficial pyoderma	4	6	1	71	60
15	Unknown	M	43	Not known	Superficial pyoderma	2	4	3	90	28
16	Unknown	F	32	2.5	Superficial pyoderma	0	4	0	60	0
17	Labrador retriever	M	29	8	Superficial pyoderma	9	4	0	47	0
18	Crossbred	M	19	9	Superficial pyoderma	8	7	7	138	99

19	Dogue de Bordeaux	M	58	2	Superficial pyoderma	8	6	3	252	79
20	Boxer	F	24	4	Superficial pyoderma	0	1	1	15	5
21	Irish Setter	M	27	5	Deep pyoderma	3	3	0	98	0
22	Crossbred	F	37	4.5	Bacterial paronychia	0	7	3	228	203
Summary	14 different breeds	11 F, 11 M	Range 4-58 (median 29)	Range 1.5-11 (median 5.4)	68.2% superficial pyoderma, 9.1% superficial and deep, 18.2% deep pododermatitis, 1 bacterial paronychia	Range 1-12 (median 3)	Range 1-11 (median 5)	Range 0-8 (median 3)	Range 14-252 (median 74)	Range 0-203 (median 53)

M: male; F: female.