
Evin R. Adolph¹, Danny W. Scott¹*, William H. Miller, Jr.¹, Hollis N. Erb²

¹Department of Clinical Sciences and ²Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University

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Abstract: Tetracycline and niacinamide (TCN) were administered to 12 dogs with discoid lupus erythematosus (DLE), 3 dogs with perianal/perivulvar lupus erythematosus (PPLE), 1 dog with vesicular cutaneous lupus erythematosus (VCLE), and 1 dog with exfoliative cutaneous lupus erythematosus (ECLE). Eight of 12 dogs (67%) with DLE and 3 of 3 dogs (100%) with PPLE were satisfactorily controlled. The dog with ECLE had a partial response, and the dog with VCLE did not respond.

Key words: dog, lupus erythematosus, niacinamide, skin, tetracycline

Introduction

Cutaneous lupus erythematosus occurs as a number of distinct clinical dermatoses in the dog³,¹⁴,²⁸. These skin disorders are uncommon to rare, and are presumed to be of immune-mediated origin. They share very similar-to-identical histopathological and immunopathological findings.

The currently recognized clinical forms of cutaneous lupus erythematosus in dogs include:

1. Systemic lupus erythematosus with lupus-specific skin lesions.
2. Discoid lupus erythematosus.
5. Perianal/perivulvar lupus erythematosus.

Systemic lupus erythematosus (SLE) is a multisystemic disorder with specific cutaneous lesions present in about 50% of the dogs²⁵,²⁷,²⁸. As the focus of this article is cutaneous (nonsystemic) lupus erythematosus, SLE will not be considered further.

Discoid lupus erythematosus (DLE) typically presents
as a nasal dermatitis characterized by depigmentation, erythema, scaling, crusting, and eventual erosion and ulceration\(^\text{10, 26-28, 30}\). It is a photoaggravated disorder often being more severe in summer months and sunny climates. Affected dogs are otherwise healthy.

Vesicular cutaneous lupus erythematosus (VCLE; formerly “idiopathic ulcerative dermatosis”) typically presents with vesicles, bullae, and polycyclic ulcers in glabrous skin areas (abdomen, groin, axillae, lateral aspect of pinnae)\(^\text{12-15, 17, 34}\). VCLE is also photoaggravated. Affected dogs are otherwise healthy. The dermatosis occurs most commonly in collies, Shetland sheepdogs, and crosses thereof.

Exfoliative cutaneous lupus erythematosus (ECLE; formerly “hereditary lupoid dermatosis”) occurs exclusively in German shorthaired pointers\(^\text{2, 3, 11, 16, 29, 32}\). More-or-less symmetrical areas of hair casts, scales, and crusts initially appear on the face and pinnae, and become increasingly widespread (exfoliative dermatitis) with time.

Perianal/perivulvar lupus erythematosus (PPLE) presents with erythema, depigmentation, erosion, and ulceration\(^\text{6, 22, 24}\). Affected dogs may exhibit dyschezia, dysuria, hematochezia, constipation, scooting, and excessive licking of affected skin.

Other rare forms of multicentric to disseminated cutaneous lupus erythematosus have been reported (“disseminated” or “generalized” DLE)\(^\text{7, 18-20}\). Affected dogs had widespread erythema, scaling, crusting, and alopecia.

Since 1992\(^\text{33}\), the combination of tetracycline and niacinamide (nicotinamide) (TCN) has been used to treat various immune-mediated and sterile granulomatous dermatoses in dogs\(^\text{1, 28, 33}\). This combination possesses numerous anti-inflammatory and immunomodulatory properties\(^\text{1, 23, 28, 33}\). One scientific article\(^\text{33}\) and anecdotal reports\(^\text{1, 8, 23, 31}\) indicate that TCN may be effective in up to 70% of the dogs with DLE.

The treatment protocol for TCN in dogs is\(^\text{33}\): 250 or 500 mg (for dogs weighing <10 or >10 kg, respectively) of each drug given orally with food every 8 hours. The combination is given with food to minimize gastrointestinal side effects (anorexia, lethargy, vomiting, and diarrhea) usually attributable to the niacinamide\(^\text{1, 8, 28, 31, 33}\). However, TCN should not be given with dairy products or vitamin/mineral supplements because divalent and trivalent cations (calcium, aluminum, magnesium, zinc, iron) bind tetracycline, thereby reducing its bioavailability\(^\text{28}\). When given with food, TCN is rarely associated with adverse effects\(^\text{1, 4, 8, 28, 31, 33}\). Anecdotal reports indicate that doxycycline (5 mg/kg given by mouth every 12 hours) can be substituted for the tetracycline.

The TCN has a slow, gradual onset of therapeutic benefit (3–8 weeks)\(^\text{1, 4, 8, 28, 31, 33}\). If a favorable response is obtained, the frequency of administration can sometimes be reduced to every 12 hours (rarely, every 24 hours)\(^\text{1, 4, 8, 28, 31, 33}\). Anecdotal reports\(^\text{1, 8, 28, 31}\) indicate that TCN may be synergistic with glucocorticoids or vitamin E.

The purpose of our article is to report the results of a retrospective study on 17 dogs with various forms of cutaneous lupus erythematosus that were treated with TCN.

### Materials and Methods

This was a retrospective study conducted on all 35 dogs with DLE seen by the Dermatology Service at the Cornell University Hospital for Animals (CUHA) from 1997-2012. Our specific data set of focus is all 12 dogs with DLE that were treated with TCN. In addition, we reviewed the medical records of dogs with VCLE (1 dog), ECLE (1 dog), and PPLE (3 dogs) that had been treated with TCN. Diagnoses were confirmed by standard historical, physical examination, and histopathological criteria\(^\text{28}\). Medical records of each dog were reviewed for the following information:

1. Signalment (age, breed, sex).
2. Duration of disease prior to examination at CUHA.
3. Prior administration of systemic glucocorticoids.
4. Response to TCN.
5. Attempts to reduce the frequency of administration of TCN treatment.
6. Follow-up period.

### Statistical Methods

Statistical analysis was only performed on dogs with DLE. We compared the animals in our case series that were mixed breeds and German shepherd dogs with the general CUHA canine population across approximately the same period. We selected the two breed groups (and no others) because these two were the most common: we wanted to focus for precision and to lessen the chance of Type-1 error from running many tests. All other breeds in the 35-dog case series had only ≤2 dogs. We also
compared the 4 sex categories (castrated male, spayed female, intact male, intact female) in our 35 dogs with the general CUHA population. These two comparisons were done using two chi-square goodness-of-fit tests (both were hand-calculated).

We obtained nonparametric descriptive statistics (because some continuous variables were right-skewed and sample size was small) for each category examined for each of the 12 DLE dogs treated with TCN. We also used simple two-by-two contingency tables to look for association (by inspection) with success of TCN treatment and several factors (including sex, prior glucocorticoid administration, and TCN dosage among others).

All statistical analyses were performed using the Statistix 9.0 program (2008 Analytical Software, Tallahassee, Florida, USA). A two-sided $P$-value of $\leq 0.01$ was considered significant for the goodness-of-fit chi-square tests. The value was chosen because $N$ was only $12^{35}$, and we were running two (i.e., multiple) tests.

**Results**

DLE (Figs. 1A and 1B) was diagnosed in 0.66% of dogs seen by the Dermatology Service from 1997-2012 (Table 1). German shepherd dogs accounted for 23% (8/35) of the dogs with DLE, but only 3.8% of the CUHA canine population ($P=<0.00001$). Mixed breed dogs accounted for 37% (13/35) of the dogs with DLE, and 24% of the CUHA canine population: however, this was not a statistically significant association. Of the 12 dogs in the TCN treatment case study, 25% (3/12) were Australian shepherds, 17% (2/12) were German shepherd dogs and 50% (6/12) were mixed breed dogs. Of the 12 dogs with DLE, ages ranged from 2.5 to 11 years (median 7 years). Weight ranged from 15 kg to 52 kg (median 30 kg).

Males and females accounted for 66% (23/35) and 34% (12/35) of all dogs with DLE, and 50% and 50% of the CUHA canine population, respectively. A sex predilection for dogs with DLE was not found ($P=0.056$). Of the 12 DLE dogs in the TCN case study, 75% (9/12) were male and 25% (3/12) were female. Duration of disease prior to examination at the CUHA varied from 0.25 to 6 years.

All DLE dogs had received a 2- to 3-week course of systemic antibiotic treatment (cephalexin, amoxicillin clavulanate, enrofloxacin) prior to being examined at the CUHA. No dog had responded.

Because DLE is a photoaggravated disease, owners were instructed to – where possible – (1) keep their dogs out of direct sunlight between 9 AM and 4 PM, and (2) apply an over-the-counter sunscreen for humans (sun protective factor >16) when direct sunlight could not be
avoided\(^\text{28}\). Sunscreen was not to be applied to ulcerated skin.

Although there were not enough cases in our case study to evaluate statistical significance, 67% (8/12: 95% confidence interval: 35%, 89%) of the 12 dogs with DLE treated with TCN had success in controlling DLE. Of the eight dogs that had success with TCN, only two did not receive glucocorticoids prior to treatment. Ten of the 12 dogs (83%) in the study received glucocorticoids (prednisone at 1 to 2 mg/kg/day, orally, for 2 to 3 weeks for 9 dogs; one dog received 0.1% betamethasone valerate ointment topically, twice daily for 4 weeks) prior to treatment with TCN.

Follow-up information was available for all 12 dogs in this study, ranging from 9 months to 5 years. Beneficial response to TCN occurred within 1 to 10 weeks. Of the eight dogs that had success with TCN treatment, 4 were successfully reduced from every 8 hours to every 12 hours. For 2 of these 4 dogs, the TCN frequency was reduced to every 24 hours, but the clinical signs recurred. Two other dogs were successfully maintained on niacinamide alone (tetracycline was stopped due to gastrointestinal side effects in 1 dog, and a pruritic papular facial dermatitis in the other).

Duration of TCN treatment in those dogs that were well-controlled ranged from 5 months to 5 years. In those dogs wherein success was not reported, TCN treatment ranged from 2.5 to 4 months. TCN doses varied from 9.6 to 33.3 mg/kg every 8 hours (median 16.7 mg/kg). TCN dosage did not appear to have any association with success or failure of therapy. Duration of disease prior to TCN treatment did not appear to have any association with success or failure of TCN treatment.

Data on the 5 dogs with VCLE (Fig. 2), ECLE (Fig. 3), and PPLE (Fig. 4) are included in Table 1. With TCN therapy, the 3 dogs with PPLE were well-controlled, and the one dog with ECLE was 75% improved. The dog with VCLE did not respond.

### Table 1. Data on dogs with DLE, VCLE, ECLE, and PPLE

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Breed</th>
<th>Duration of Disease (years)</th>
<th>Duration of follow-up (years)</th>
<th>Positive response to TCN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discoid Lupus Erythematosus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>FS</td>
<td>Australian shepherd</td>
<td>3</td>
<td>5</td>
<td>Yes, every 8 hours</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>MC</td>
<td>Mixed breed</td>
<td>–</td>
<td>2.5</td>
<td>Yes*</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>MC</td>
<td>German shepherd</td>
<td>1</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>MC</td>
<td>Australian shepherd</td>
<td>3</td>
<td>1.5</td>
<td>Yes†</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>MC</td>
<td>Australian shepherd</td>
<td>0.25</td>
<td>4.5</td>
<td>Yes, every 12 hours</td>
</tr>
<tr>
<td>6</td>
<td>4.5</td>
<td>MC</td>
<td>German shepherd dog</td>
<td>1</td>
<td>3</td>
<td>Yes, every 12 hours</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>MC</td>
<td>Mixed breed</td>
<td>0.25</td>
<td>2</td>
<td>Yes, every 12 hours</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>MC</td>
<td>Samoyed</td>
<td>1</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>MC</td>
<td>Mixed breed</td>
<td>6</td>
<td>1</td>
<td>Yes, every 12 hours</td>
</tr>
<tr>
<td>10</td>
<td>7.5</td>
<td>MC</td>
<td>Mixed breed</td>
<td>1</td>
<td>5</td>
<td>Yes, every 8 hours</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>FS</td>
<td>Mixed breed</td>
<td>0.75</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>FS</td>
<td>Mixed breed</td>
<td>3</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td><strong>Vesicular Cutaneous Lupus Erythematosus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>F</td>
<td>Shetland sheepdog</td>
<td>0.5</td>
<td>0.25</td>
<td>No</td>
</tr>
<tr>
<td><strong>Exfoliative Cutaneous Lupus Erythematosus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>14</td>
<td>6</td>
<td>FS</td>
<td>German shorthaired pointer</td>
<td>1</td>
<td>3.5</td>
<td>Yes, every 12 hours</td>
</tr>
<tr>
<td><strong>Perianal/Perivulvar</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>FS</td>
<td>Miniature pinscher</td>
<td>0.5</td>
<td>1</td>
<td>Yes, every 8 hours</td>
</tr>
<tr>
<td>16</td>
<td>4.5</td>
<td>FS</td>
<td>German shepherd dog</td>
<td>0.5</td>
<td>5.5</td>
<td>Yes, every 24 hours</td>
</tr>
<tr>
<td>17</td>
<td>9</td>
<td>FS</td>
<td>German shepherd dog</td>
<td>4</td>
<td>2</td>
<td>Yes, every 24 hours</td>
</tr>
</tbody>
</table>

F = Intact female; FS = Neutered female; MC = Neutered male.

*Case 2 was treated with niacinamide every 12 hours as tetracycline caused a pruritic papular facial dermatitis.

†Case 4 was treated with niacinamide every 12 hours, as tetracycline caused gastrointestinal side effects.
Discussion

DLE accounted for 0.66% of the canine dermatology cases examined at the CUHA from 1997-2012. This percentage is higher than the 0.3% reported in our clinic in the 1980s\(^2\). Previous studies have reported that DLE is most commonly seen in collies, Shetland sheepdogs, German shepherds, Siberian huskies, and Brittany spaniels\(^{21, 26, 27}\). Our study confirms a breed association for German shepherds. There was no sex predilection for DLE in our study, although previous studies have suggested that females\(^{26, 27}\) or males\(^{21}\) were predilected. Age of onset of DLE ranged from 2.5 to 11 years in our study, which is in agreement with previous studies\(^{21, 26, 27}\).

Canine DLE typically requires life-long therapy\(^{28}\). There are various methods of treatment for canine DLE, mainly involving the use of immunomodulatory drugs: glucocorticoids (systemic and/or topical), azathioprine, chlorambucil, cyclosporine, vitamin E, and topical tacrolimus\(^{7-9, 21, 26-28, 31, 33}\). Because DLE is a photoaggravated disease, treatments are typically used in conjunction with photoavoidance and/or photoprotection\(^{28}\).

Since 1992\(^{33}\), the combination of tetracycline – or doxycycline – and niacinamide has been reported to be useful for the management of canine DLE\(^{1, 8, 28, 31}\). In the initial report by White \textit{et al.}\(^{33}\), 70% of the dogs were satisfactorily controlled with TCN. Our study – wherein 67% of the dogs were satisfactorily controlled – corroborates the findings of White \textit{et al.}\(^{33}\). In addition – as reported by White \textit{et al.}\(^{33}\) – we found that prior glucocorticoid therapy did not appear to determine success or failure of subsequent treatment with TCN. Initial beneficial responses to TCN in our study were noted within 1 to 10 weeks of treatment, which is consistent with the observations of others\(^{1, 8, 28, 31} \). We found no apparent association between the dose of TCN (9.6 to 33.3 mg/kg every 8 hours) and the success or failure of treatment. This was also reported in a study on the efficacy of TCN in the treatment of superficial pemphigus in dogs\(^4\).

Anecdotal reports indicated that the frequency of administration of TCN for canine DLE could “often” be reduced to every 12 or 24 hours, and that tetracycline was rarely effective when administered alone\(^{1, 8, 28, 31}\). In our study, the frequency of TCN administration was successfully reduced to every 12 hours in 4 dogs. In 2
of these dogs, the frequency of TCN administration was reduced to every 24 hours, but both dogs relapsed. We also had 2 dogs that had adverse reactions to tetracycline and were successfully managed with niacinamide alone. This has not been previously reported.

It is not clear why some dogs with DLE respond to a given therapeutic protocol and others do not. However, potential advantages of using TCN for the treatment of DLE, as compared to glucocorticoids and other potent agents, include similar efficacy, safety (rare acute and chronic side effects), and economy (TCN are inexpensive; frequent follow-up blood work not necessary).

Little information is published on the use of TCN in other forms of cutaneous lupus erythematosus. TCN was reported to be ineffective in one dog with VCLE\(^\text{13}\), and our one case also failed to respond.

ECLE is notoriously resistant to therapy (glucocorticoids, azathioprine, vitamin A, essential fatty acids, cyclosporine, hydroxychloroquine, adalimumab)\(^\text{3,16,29}\). TCN was only temporarily effective or ineffective in 7 dogs\(^\text{3,29}\). In our dog, TCN every 12 hours provided a 75% reduction in clinical signs for 3.5 years.

PPLE has been reported to respond satisfactorily to prednisolone, prednisolone with azathioprine or chlorambucil, or TCN\(^\text{6,22,24}\). All 3 of our dogs responded well to TCN. Two of them were satisfactorily controlled with TCN every 24 hours.

It is not clear why TCN is often successful for the management of DLE and PPLE, but not VCLE and ECLE. Perhaps part of the reason for this is that DLE and PPLE are localized diseases, while VCLE and ECLE are widespread.

One concern over the long-term administration of tetracycline, or any antimicrobial agent, is the emergence of drug-resistant strains of bacteria. To our knowledge, this has not been reported with the long-term use of TCN in dogs and humans.

In conclusion, we found the combination of tetracycline and niacinamide (TCN) to be a useful therapeutic approach to canine DLE and canine PPLE. Because of the slow onset of action of TCN (1 to 10 weeks) in canine DLE and PPLE, other therapeutic agents (systemic or topical glucocorticoids, topical tacrolimus) might be required during the first few weeks of treatment\(^\text{1,8,28,31}\).

References

and Microscopic Evaluation of Canine and Feline Skin Diseases, C.V. Mosby, St. Louis.