Relationship between Degenerative Joint Disease, Pain, and Bartonella spp. Seroreactivity in Domesticated Cats

A. Tomas, E.L. Pultorak, M.E. Gruen, E.B. Breitschwerdt, and B.D.X. Lascelles

**Background:** Recently, a potential association was identified between Bartonella exposure and arthritides in mammalian species other than cats.

**Hypothesis/Objectives:** We hypothesized that Bartonella exposure is associated with more severe degenerative joint disease (DJD) and a greater burden of DJD-associated pain in client-owned cats.

**Animals:** Ninety-four client-owned cats (6 months to 20 years old), ranging from clinically unaffected to severely lame because of DJD.

**Methods:** Using physical examination and radiography, pain and radiographic scores were assigned to each part of the bony skeleton. Sera were tested for Bartonella henselae, B. koehlerae, and B. vinsonii subsp. berkholzii (genotypes I, II, and III) antibodies using immunofluorescence antibody assays. Variables were categorized and logistic regression used to explore associations.

**Results:** Seropositivity to Bartonella was identified in 33 (35.1%) cats. After multivariate analysis controlling for age, total DJD score (OR, 0.51; 95% CI, 0.26–0.97; \( P = .042 \)), appendicular pain score (OR, 0.33; 95% CI, 0.17–0.65; \( P = .0011 \)), and total pain score (OR, 0.35; 95% CI, 0.17–0.72; \( P = .0045 \)) were significantly inversely associated with Bartonella seroreactivity status, indicating that cats with higher DJD and pain scores were less likely to be Bartonella seropositive.

**Conclusions and Clinical Importance:** Based upon this preliminary study, Bartonella spp. seropositivity was associated with decreased severity of DJD and decreased DJD-associated pain in cats. Additional studies are needed to verify these findings, and if verified, to explore potential mechanisms.

**Key words:** Bartonella spp.; Cats; Degenerative joint disease; Pain; Radiographic; Seroreactivity.

Research over the last 10 years has highlighted the high prevalence of radiographic evidence of degenerative joint disease (DJD) in cats1–4 and has shown that a spectrum of clinical signs can be associated with DJD in cats.5–7 Most authors agree that the prevalence of DJD in cats is strongly and positively associated with age.2,4 Other work has shown that in association with the increase in radiographic DJD, musculoskeletal pain increases, whereas mobility and the ability to perform activities decreases.2,8

Despite the high prevalence, currently, little is known about the etiology of DJD in cats.9 Recently, based upon gene microarray data, immune system dysregulation was found to be associated with DJD in cats,10 but the relationship between is not clear.

There is increasing interest in the potential role of systemic infections in the etiology of joint disease in mammals. In dogs, synovial specimens from 43 dogs diagnosed with degenerative rupture of the cranial cruciate ligament were tested for presence of bacterial DNA.11 Of those, 37% were found to be PCR positive with mixtures of environmental bacterial nucleic acids found. In their discussion, the authors suggested that these bacterial mixtures or their products could promote the development of synovitis. Additional work by the group suggested that bacterial load is unlikely to be a primary pro-inflammatory factor, but the authors suggested dysregulation of immune responses within synovial tissues might be dependent upon an environmental microbial trigger.12 Bartonella spp. have been implicated as a cause of lameness. One study in dogs evaluated the relationship between lameness and seroprevalence of Bartonella spp. antibodies, and found a positive association between lameness and arthritis-related lameness and Bartonella spp. seroreactivity.13 It has also been suggested that immune dysregulation occurs in dogs experimentally infected with Bartonella vinsonii subsp. berkholzii genotype I, which could predispose these dogs to autoimmune or immune-mediated diseases such as polyarthritis.14
horses, 1 study found a high prevalence of *Bartonella* spp. bacteremia in lame horses as compared to controls. In an uncontrolled study, 62% of 296 human patients selected by a rheumatologist for testing were found to be positive for antibodies against *Bartonella* spp.6

Despite these findings in other species, the high prevalence of DJD in cats, and the fact that cats are the natural host for *Bartonella*, to the authors’ knowledge, no studies have evaluated if there is any relationship between DJD and associated pain and *Bartonella* exposure in cats. On the basis of the findings in other species, we hypothesized that *Bartonella* spp. seropositivity in cats is associated with more severe radiographic DJD and a greater burden of DJD-associated pain. The aim of this study was to explore a potential relationship between radiographic DJD, pain assessed on palpation during orthopedic evaluation and *Bartonella* spp. seropositivity in a population of domestic cats.

**Materials and Methods**

Samples were collected for this study under clinical research protocols approved by the Institutional Animal Care and Use Committee at North Carolina State University College of Veterinary Medicine (NCSU-CVM) (IACUC numbers 05-020-O and 06-056-O). Informed owner consent was granted in each case.

**Animals**

This observational study used samples taken from cats (n = 100) recruited for an earlier study evaluating the prevalence of DJD, as previously described6, and samples taken from cats (n = 12) recruited to a study evaluating the efficacy of a diet for the alleviation of DJD-associated pain.15 Cats from the latter study were included if they had been screened in exactly the same manner as for the former study.

**Demographic and Clinical Data Collected**

Data collected included: age, weight, sex, body condition score, vaccination status [rabies, feline leukemia virus (FeLV), feline viral rhinotracheitis, calicivirus and panleukopenia (FVRCP)], current tick and flea prevention status, appetite, and whether or not there were other cats in the household. In addition, the owners were asked if they thought their cat had arthritis (yes/no response).

Orthopedic examination of the appendicular and axial skeleton was performed for all cats by a single investigator (BDXL). The degree of musculoskeletal pain in response to palpation of each appendicular joint and each segment of the axial skeleton was graded as previously described8 using a numerical rating scale: 0 = no resentment; 1 = mild withdrawal, mildly resist; 2 = moderate withdrawal, body tenses, might orient to site, might vocalize, hiss or bite; 3 = orients to site, forcible withdrawal from manipulation, might vocalize, hiss or bite; 4 = tries to escape or prevent manipulation, hisses or bites, marked guarding of the area. Scores were summed across all appendicular joints (appendicular pain score; maximum score, 64), each part of the axial skeleton (axial pain score; maximum score, 16) and a total pain score calculated from the sum of these 2 (total pain score; maximum score, 80).

In addition, a temperament score was given to each cat as previously described8 with 0 = neutral attitude, purring, kneading; 1 = resistance to restraint; 2 = resistance to restraint, growling and hissing; 3 = resistance with biting and scratching, vocalizing and hissing and 4 = resistance with biting, scratching, vocalizing, hissing, urinating or defecating. The temperament score was assigned by a single investigator (BDXL) in all cases, and was assigned after completion of the examination.

Radiographic examination was performed as previously described.8 Scores for severity of defined radiographic features were allocated to each appendicular joint and an overall score on a 0–10 scale assigned to each joint. These overall scores for each joint were summed to create an appendicular DJD score (appendicular DJD score; maximum score, 160). Scores likewise were allocated to each segment of the axial skeleton and summed to create an axial skeleton DJD score (axial DJD score; maximum score, 40). Addition of the appendicular DJD and axial DJD scores created a total DJD score (total DJD score; maximum score, 200). Features that were evaluated have been previously described in detail.8

**Evaluation of Bartonella spp. Seroreactivity**

*Bartonella henselae*, B. koehlerae, and B. vinsonii subsp. berkhoffii (genotypes I, II, and III) antigens were used with traditional immunofluorescence antibody assay (IFA) methods using fluorescein-conjugated goat anti-cat IgG (Pierce Antibody) to determine the antibody titer to each *Bartonella* sp. or subspecies.18 Briefly, isolates of *B. henselae* (strain Houston-1, ATCC #49882), B. koehlerae (NCSU FO-1-09) and B. vinsonii subsp. berkhoffii genotype I (NCSU isolate 93-CO-1, ATCC #51672), II (NCSU isolate 95-CO-2) and genotype III (NCSU isolate 06-COI) were passed from agar-grown cultures into *Bartonella*-permissive tissue culture cell lines (AAE12 [an embryonic Amblyommia americanum tick cell line] for *B. henselae*, Vero (a mammalian fibroblast cell line) for the *B. vinsonii* genotypes, and DH82 (a canine monocyto-toid cell line) for *B. koehlerae*) to obtain intracellular whole bacteria antigens for IFA testing. Heavily infected cell cultures were spotted onto 30-well Teflon-coated slides (Cel-Line®) air-dried, acetone fixed, and stored frozen. Serum samples were diluted in phosphate-buffered saline (PBS) solution containing normal goat serum, Tween-20, and powdered nonfat dry milk to block non-specific antigen binding sites and incubated on antigen slides. All available patient sera were screened at dilutions of 1 : 16 to 1 : 64. All sera that were reactive at a 1 : 64 dilution were further tested with 2-fold dilutions out to 1 : 8,192. A threshold titer of 1 : 64 was used to define a seroreactive (seropositive) antibody response against a specific *Bartonella* sp. antigen.

**Statistical Analysis**

Descriptive statistics were used to describe *Bartonella* spp. seroreactivity; number of cats with radiographic DJD and musculoskeletal pain in the appendicular and axial skeleton; summed severity for total DJD and total pain in each cat; physical examination findings related to pain and DJD; and demographic characteristics of the population, including owner assessment of whether or not they thought the cat had arthritis and the number of cats previously living with other cats. Comparisons were made to evaluate associations between each variable (including DJD score, pain scores, demographic characteristics, and clinical features) and *B. henselae*, B. koehlerae, and B. vinsonii subsp. berkhoffii seropositivity separately, in addition to a composite variable for seropositivity to any of the 3 *Bartonella* sp. antigens. Variables with >5% missing values were not included in the analyses to avoid potential exclusion biases for cats with missing data. Total DJD scores were grouped into approximate tercile categories: low (0–5), moderate (6–17), and high (18–41) scores. Similarly, total pain scores were
grouped into categories: low (0–2), moderate (3–10), and high (11–45) scores. Axial and appendicular pain and DJD scores were categorized also into approximate terciles: axial pain: low (0), moderate (1–2), and high (2–13) scores; appendicular pain: low (0–1), moderate (2–5), and high (6–33) scores; axial DJD: low (0), moderate (1–3), and high (4–23) scores; appendicular DJD: low (0–4), moderate (5–13), and high (14–34) scores. All terciles were created to correspond to approximate clinical designations of low, moderate and severe DJD or pain based on clinical experience. Univariate analysis was carried out using the chi-square or Fish-er’s exact test for 2 × 2 comparisons, and the Mann-Whitney-Wilcoxon test for continuous comparisons to assess associations between each variable and Bartonella spp. or sp. seropositivity status. The categorical variables of total, axial, and appendicular DJD and pain scores, were entered individually into logistic regression analysis while controlling for age (ie, DJD score and pain score were not entered into the model at the same time). Age was categorized into 3 levels: 0–4.99 years, 5–9.99 years, and ≥10 years. Four outcome variables included: B. henselae seroreactivity, B. koehlerae seroreactivity, B. vinsonii subsp. berkholffii seropositivity, and seropositivity to any of the 3 Bartonella sp. antigens. Significance was set at P ≤ .05. Statistical analyses were performed using SAS/STAT 9.2 for Windows.b

Results

One-hundred and twelve cats were included in this study; 18 cats were excluded from analysis because of missing values related to DJD score, pain score, or Bartonella spp. seroreactivity status as described in the Materials and Methods section. Of the 100 cats, 112 were included in the analysis. The median age in years was 9.26 (range, 1.03–19.89), and median body weight was 4.78 kg (range, 2.08–10.16). Median appetite score was 85.9 (range, 0–100). Temperament score distributions were 0 in 43.6% of the cats, 1 in 19.2%, 2 in 13.8%, 3 in 21.3% to 4 in 2.1% of cats. Seventy-four (78.7%) cats had lived previously with other cats. Owners of 32 cats (34.0%) indicated they considered the cat had arthritis, compared to 42.6% of cats with owners that did not think the cat had arthritis (OR, 0.25; CI, 0.07–0.85). Univariate analysis identified the following variables as significantly inversely associated with Bartonella spp. seropositivity: B. henselae DJD score (P = .022), appendicular pain score (P = .0016), and total pain score (P = .0063). Appendicular DJD score (P = .19), axial DJD score (P = .12), and axial pain score (P = .13) were not significantly associated with Bartonella spp. seropositivity in univariate analysis (P = .020). Interestingly, in only 18.2% (n = 6) of Bartonella spp. seropositive cats did owners consider the cat had arthritis, compared to 42.6% (n = 26) of seronegative cats. After controlling for age, this association remained significant (P = .027), and indicated that cats with owners that considered the cat to have arthritis were 3.97 times more likely to be Bartonella spp. seronegative than cats with owners who did not think the cat had arthritis (OR, 0.25; CI, 0.07–0.85).

Based on IFA antibody testing, seropositivity to B. henselae, B. koehlerae, or B. vinsonii subsp. berkholffii was identified in 33 (35.1%) cats. Titters ranged from <1:16 to 1:1024. Fourteen (14.9%) cats were seropositive to B. henselae seropositive, 26 (27.6%) were B. koehlerae seropositive, and 20 (21.3%) were seropositive to B. vinsonii subsp. berkholffii antigens. Of the 33 seropositive cats, 19 were seropositive to multiple Bartonella spp. antigens (57.6%). Bartonella spp. seropositivity did not vary by age (P = .13), sex (P = .89), body weight (<4.78 kg versus ≥4.78 kg; P = .27), temperament (P = .97), appetite (P = .09), flea and tick prevention status (P = .86), or whether or not there were other cats in the household (P = .78).

Whether owners thought their cats had arthritis varied by Bartonella spp. seropositivity in univariate analysis (P = .020). Interestingly, in only 18.2% (n = 6) of Bartonella spp. seropositive cats did owners consider the cat had arthritis, compared to 42.6% (n = 26) of seronegative cats. After controlling for age, this association remained significant (P = .027), and indicated that cats with owners that considered the cat to have arthritis were 3.97 times more likely to be Bartonella spp. seronegative than cats with owners who did not think the cat had arthritis (OR, 0.25; CI, 0.07–0.85). Univariate analysis identified the following variables as significantly inversely associated with Bartonella spp. seropositivity: B. henselae DJD score (P = .022), appendicular pain score (P = .0016), and total pain score (P = .0063). Appendicular DJD score (P = .19), axial DJD score (P = .12), and axial pain score (P = .13) were not significantly associated with Bartonella spp. seropositivity in univariate analysis (P = .020). Interestingly, in only 18.2% (n = 6) of Bartonella spp. seropositive cats did owners consider the cat had arthritis, compared to 42.6% (n = 26) of seronegative cats. After controlling for age, this association remained significant (P = .027), and indicated that cats with owners that considered the cat to have arthritis were 3.97 times more likely to be Bartonella spp. seronegative than cats with owners who did not think the cat had arthritis (OR, 0.25; CI, 0.07–0.85). Univariate analysis identified the following variables as significantly inversely associated with Bartonella spp. seropositivity: B. henselae DJD score (P = .022), appendicular pain score (P = .0016), and total pain score (P = .0063). Appendicular DJD score (P = .19), axial DJD score (P = .12), and axial pain score (P = .13) were not significantly associated with Bartonella spp. seropositivity in univariate analysis (P = .020). Interestingly, in only 18.2% (n = 6) of Bartonella spp. seropositive cats did owners consider the cat had arthritis, compared to 42.6% (n = 26) of seronegative cats. After controlling for age, this association remained significant (P = .027), and indicated that cats with owners that considered the cat to have arthritis were 3.97 times more likely to be Bartonella spp. seronegative than cats with owners who did not think the cat had arthritis (OR, 0.25; CI, 0.07–0.85).
Table 1. *Bartonella* seroreactivity in association with total degenerative joint disease (DJD) scores and total pain scores after univariate analysis.

| Seroreactivity                      | DJD Total                   | Pain Total                    |
|-------------------------------------|-----------------------------|-------------------------------|
|                                     | Low            | Moderate | High  | P-Value | Low            | Moderate | High  | P-Value |
| *Bartonella* spp. composite sero+  | 14 (42.2)  | 14 (42.2) | 5 (15.2) | .022 | 18 (54.5)  | 13 (39.4) | 2 (6.1) | .0063  |
| *Bartonella* spp. composite sero−  | 19 (31.2)  | 15 (24.6) | 27 (44.3) | .89 | 18 (29.5)  | 24 (39.3) | 19 (31.2) |                      |
| *B. henselae* sero+                | 7 (50.0)    | 5 (35.7)  | 2 (14.3)  | .22 | 8 (57.2)   | 5 (35.7)  | 1 (7.2)  | .19    |
| *B. henselae* sero−                | 26 (32.5)  | 24 (30.0) | 30 (37.5) | .14 | 28 (35.0)  | 32 (40.0) | 20 (25.0) | .028   |
| *B. koehlerae* sero+               | 10 (38.5)  | 11 (42.3) | 5 (19.2)  | .13 | 15 (57.7)  | 9 (34.6)  | 2 (7.7)  | .0063  |
| *B. koehlerae* sero−               | 23 (33.8)  | 18 (26.5) | 27 (39.7) | .14 | 21 (30.8)  | 28 (41.2) | 19 (27.9) |                      |
| *B. vinsonii* subsp. berkoffii sero+| 9 (45.0)   | 8 (40.0)  | 3 (15.0)  | .022| 10 (50.0)  | 9 (45.0)  | 1 (5.0)  | .0063  |
| *B. vinsonii* subsp. berkoffii sero−| 24 (32.4)  | 21 (28.4) | 29 (39.2) | .02 | 26 (35.2)  | 28 (37.8) | 20 (27.0) |                      |

Numbers indicate the number of cats in each DJD or Pain designation that were seropositive (sero+) or seronegative (sero−) for each *Bartonella* spp., and for any of the three *Bartonella* spp. (composite). Numbers indicate the number of cats and numbers in brackets indicate the percentage distribution within the designation of sero+ or sero− for either DJD or Pain.

Table 2. *Bartonella* seroreactivity in association with total degenerative joint disease (DJD) scores, appendicular DJD scores, and axial DJD scores after multivariate analysis.

| Seroreactivity                      | Total DJD OR (95% CI; P-Value) | Appendicular DJD | Axial DJD |
|-------------------------------------|---------------------------------|------------------|-----------|
| *B. henselae*                       | 0.46 (0.19–1.11; P = .085)      | 0.41 (0.17–0.98; P = .046) | 0.59 (0.26–1.41; P = .24) |
| *B. koehlerae*                      | 0.75 (0.38–1.48; P = .42)       | 0.86 (0.45–1.63; P = .64) | 0.55 (0.28–1.11; P = .095) |
| *B. vinsonii* subsp. berkoffii      | 0.54 (0.25–1.16; P = .11)       | 0.75 (0.37–1.52; P = .42) | 0.77 (0.37–1.06; P = .48) |
| *Bartonella* spp. composite        | 0.51 (0.26–0.97; P = .042)      | 0.72 (0.40–1.32; P = .29) | 0.53 (0.86–1.03; P = .062) |

Odds ratios (and 95% confidence intervals) are shown in relation to seroreactivity to *B. henselae; B. koehlerae; and B. vinsonii* subsp. *berkoffii,* and a composite *Bartonella* variable representing seroreactivity to any of the three species.

Table 3. *Bartonella* seroreactivity in association with total pain, appendicular pain, and axial pain scores after multivariate analysis.

| Seroreactivity                      | Total Pain OR (95% CI; P-Value) | Appendicular Pain | Axial Pain |
|-------------------------------------|---------------------------------|------------------|-----------|
| *B. henselae*                       | 0.42 (0.16–1.09; P = .075)      | 0.65 (0.29–1.42; P = .27) | 0.45 (0.29–1.42; P = .081) |
| *B. koehlerae*                      | 0.39 (0.18–0.84; P = .017)      | 0.49 (0.26–0.95; P = .033) | 0.50 (0.26–0.96; P = .037) |
| *B. vinsonii* subsp. berkoffii      | 0.49 (0.22–1.09; P = .083)      | 0.42 (0.20–0.89; P = .024) | 0.82 (0.44–1.53; P = .54) |
| *Bartonella* composite              | 0.35 (0.17–0.72; P = .0045)     | 0.33 (0.17–0.65; P = .0011) | 0.62 (0.35–1.07; P = .087) |

Odds ratios (and 95% confidence intervals) are shown in relation to seroreactivity to *B. henselae; B. koehlerae; and B. vinsonii* subsp. *berkoffii,* and a composite *Bartonella* variable representing seroreactivity to any of the three species.

**Discussion**

In this study, we found that cats with higher DJD and pain scores were less likely to be *Bartonella* seropositive than cats with lower scores, thus rejecting our hypothesis that *Bartonella* exposure is associated with more severe DJD and a greater burden of musculoskeletal pain. Even after controlling for age, the association between *Bartonella* seronegativity and increased DJD and pain scores remained significant. However, it is possible that unmeasured confounders such as immune status, arthropod exposure and other infections could impact the observed associations. These findings are surprising and require additional study.

Radiographic evidence of DJD and pain responses on manipulation of the skeleton are not necessarily measures of the same thing. Previous work by our group has indicated that the detection of joint pain had poor sensitivity for the detection of radiographic DJD, and also had poor positive predictive value. This is not surprising given that clinical signs and radiographic severity are not closely related in humans with DJD. Radiographic signs of DJD relate to 1 aspect of the disease, and pain scores relate to another (ie, to the current clinical impact of the disease). Obviously, there must be a relationship between the 2, but at a given point in time the burden of radiographic disease in a given joint might not match the burden of pain. Thus, in order to more completely assess the relationship between *Bartonella* seropositivity and DJD in cats, we, a priori, set out to look at both pain and radiographic DJD. Appendicular DJD refers to synovial joints, and axial DJD to a combination of some synovial joints (facets) and intervertebral disk joints. Overall, appendicular and axial DJD could be considered to represent 2 different pathologies, but the
pathogenesis of appendicular and axial DJD in the cat is largely unknown.9 Interestingly, our data did not indicate any association between Bartonella seropositivity and DJD or between DJD (except for some individual Bartonella sp. associations), only with the total DJD score. On the basis of the consistency of the significant associations we found across our data, our results appeared to indicate a more robust association between Bartonella seropositivity and radiographic DJD scores than between seropositivity and lower radiographic DJD scores.

Our results were opposite of what we expected to find, and it is important to consider all explanations. Firstly, although these findings are provocative, the results are from 1 study, and these results should be replicated in order to be more certain they do not reflect Type I error. Importantly, we did not correct for multiple comparisons within the factors being evaluated (eg, DJD, pain) and this increases the likelihood of finding significant associations. We believe our approach was appropriate for an exploratory study. Other factors we did not consider might be important confounders, such as age. For example, DJD might have altered the cats’ behavior, making them less likely to be exposed to Bartonella. Conversely, a lack of pain might have altered the cats’ behavior making them more likely to roam and become exposed to Bartonella.

Other investigators have found surprising associations between Bartonella sp. seropositivity in cats and disease states. In a study investigating B. henselae seroprevalence in cats with clinical signs of neurologic disease,22 the authors found that the prevalence of Bartonella spp. antibodies was significantly lower in the group of cats with neurologic manifestations than in healthy cats with or without neurologic signs. The authors discussed various explanations for this finding, including the possibility that antibodies might not accurately indicate exposure to or infection with B. henselae. Because neurobartonellosis is a well-recognized entity in human patients,22 the authors suspected an association between neurologic disease and bartonellosis. In another study, the prevalence of Bartonella spp. antibody titers in cats with gingivitis and stomatitis (37/70 (52.9%)) was slightly lower than in the healthy control cats (36/61 (59.0%)), but this difference was not significant.24 In a different study, in which both antibody status and bacteremia were assessed, only bacteremia was significantly associated with gingivitis and stomatitis.25 In a study evaluating Bartonella spp. seroprevalence in cats with or without uveitis, the investigators found that healthy cats were significantly more likely to be Bartonella spp. seropositive than cats with uveitis and healthy cats were more likely to have higher antibody titers than cats with uveitis and cats with nonocular disease.26 Collectively, in conjunction with the results of this study, there is a body of observational evidence indicating that seropositivity to Bartonella spp. appears to be associated with decreased radiographic DJD, musculoskeletal pain, neurologic disease, gingivitis, stomatitis and uveitis. These studies do not indicate a cause-and-effect relationship, simply an inverse relationship between Bartonella spp. seropositivity and certain diseases. If there is a cause-and-effect relationship, establishing the mechanisms ultimately could lead to substantial preventive care, medical treatment, or both.

Bartonella spp. have been associated with various serious diseases in cats (eg, endocarditis,27 osteomyelitis,28 and myocarditis29), and there is continued discussion on what a “Bartonella sp. seropositive” result actually means in terms of prior exposure or ongoing infection.

The flea, the cat, and Bartonella have co-existed for so long that it is possible Bartonella spp. and the cat have co-evolved over time and there is some benefit to both species of this coexistence. Most studies of Bartonella in cats refer to cats as the natural reservoir of B. henselae and B. claridgeiae, and discuss medical implications of infection in cats with other Bartonella spp. Recent evidence indicates that there is variation in virulence among B. henselae strains, with most strains found in cats differing genetically from the strains that initially cat scratch day 1. For example, the prevalence of Bartonella spp. bacteremia (most often because of B. henselae or B. claridgeiae), can be ≥50% or in feral cats or cats with extensive arthropod exposure. The majority of these cats do not have any clinical disease associated with a Bartonella. However, it is clear that some strains of B. henselae are highly pathogenic in cats.29

If this finding of an association between seropositivity to Bartonella spp. and decreased burden of DJD and musculoskeletal pain is eventually proven to be a causative association, it is likely a complex immune response occurring after Bartonella spp. exposure that will be the modulating factor in the development of DJD and musculoskeletal pain. Unfortunately, very little is known about the etiology of DJD in cats,30 the mechanisms of long-term musculoskeletal pain in cats, and it is too early to postulate what these mechanisms might be. It was recently shown that B. quintana lipopolysaccharide (LPS) is a potent Toll Like Receptor-4 (TLR-4) antagonist31 suggesting B. quintana LPS might prove useful as a potent anti-TLR-4 agent with therapeutic potential in both infections and autoimmune inflammation. The same group found that inhibition of TLR-4 suppresses the severity of arthritis in an experimental model of an immune-based arthritis (ie, collagen-induced arthritis) and resulted in lower IL-1 expression in arthritic joints, and they suggested that TLR-4 might be a novel target in the treatment of rheumatoid arthritis.30 However, this rodent model was an experimental immune-based arthritis, and might not reflect naturally occurring DJD in cats. With regard to pain, there is increasing evidence that TLRs and their associated signaling components contribute to pain hypersensitivity, and that blockade of TLR signaling can decrease pathologic pain and hypersensitivity,31 including that in rodent models of immune-mediated arthritis.32 However, these rodent
models of immune-mediated arthritis may not reflect DJD in cats.

Additional work is needed to understand the mechanisms of DJD and long-term musculoskeletal pain in cats, and to evaluate whether or not there are immunologic differences between seroreactive and nonseroreactive cats and whether these differences might relate to the observations seen in this study.

One of the limitations of this study is that we used cats from a restricted geographic area, and the majority of the cats in our study were under the care of an exclusively feline only practice. The seroprevalence of Bartonella spp. varies across different regions of North America, and it would be useful to repeat this study in different geographical areas and determine if the relationships remain. Additionally, this work should be repeated in a more diverse local population of cats.

The results of our study add to a small body of work reporting associations between Bartonella seropositivity and decreased disease burden across several diseases. Breitschwerdt and Lappin wrote “comprehensive, sequential, long term studies will be necessary to establish whether cats pay a ‘biologic price’ when chronically bacteremic with a Bartonella species.” Although this is true, we suggest that some cats may gain a “biologic benefit” from Bartonella spp seropositivity.

Footnotes

a Thermo Fisher Scientific, Rockford IL
b SAS Institute Inc, Cary, NC

Acknowledgments

The authors are grateful to Julie Bradley for serological testing and Barbara Hegarty for preparation of diagnostic antigens. This research was funded by Novartis Animal Health Fellowship Research Program (Sample collection and demographic data acquisition), and by donations to the Vector Borne Diseases Research Fund, North Carolina Veterinary Medical Foundation. Beth Pultorak’s Ph.D. is funded by Bayer Animal Health. ME Gruen received funding from the NIH Ruth L. Kirschstein National Research Service Award T32OD011130.

Conflict of Interest Declaration: In conjunction with Dr. Sushama Sontakke and North Carolina State University, Dr. Breitschwerdt holds U.S. Patent No. 7,115,385, Media and Methods for cultivation of microorganisms, which was issued October 3, 2006. He is the chief scientific officer for Galaxy Diagnostics, a newly formed company that provides advanced diagnostic testing for the detection of Bartonella species infection in animals.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

References

1. Hardie EM, Roe SC, Martin FR. Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994–1997). J Am Vet Med Assoc 2002;220:628–632.
2. Lascelles BD, Henry JB 3rd, Brown J, et al. Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. Vet Surg 2010;39:535–544.
3. Clarke SP, Mellor D, Clements DN, et al. Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats. Vet Rec 2005;157:793–799.
4. Slingerland LI, Hazewinkel HA, Meij BP, et al. Cross-sectional study of the prevalence and clinical features of osteoarthritis in 100 cats. Vet J 2011;187:304–309.
5. Guillot M, Moreau M, Heit M, et al. Characterization of osteoarthritis in cats and meloxicam efficacy using objective chronic pain evaluation tools. Vet J 2013;196:360–367.
6. Benito J, Hansen B, Depuy V, et al. Feline musculoskeletal pain index: Responsiveness and testing of criterion validity. J Vet Intern Med 2013;27:474–482.
7. Lascelles BD, Hansen BD, Roe S, et al. Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis. J Vet Intern Med 2007;21:410–416.
8. Lascelles BD, Dong YH, Marcellin-Little DJ, et al. Relationship of orthopedic examination, goniometric measurements, and radiographic signs of degenerative joint disease in cats. BMC Vet Res 2012;8:10.
9. Lascelles BD. Feline degenerative joint disease. Vet Surg 2010;39:2–13.
10. Gao X, Lee J, Malladi S, et al. Feline degenerative joint disease: A genomic and proteomic approach. J Feline Med Surg 2013;15:466–477.
11. Muir P, Oldenhoff WE, Hudson AP, et al. Detection of DNA from a range of bacterial species in the knee joints of dogs with inflammatory knee arthritis and associated degenerative anterior cruciate ligament rupture. Microb Pathog 2007;42:47–55.
12. Schwartz Z, Zitzer NC, Racette MA, et al. Are bacterial load and synovitis related in dogs with inflammatory stifle arthritis? Vet Microbiol 2011;148:308–316.
13. Jenn JB, Liu CH, Kasten RW, et al. Seroprevalence of antibodies against Bartonella species and evaluation of risk factors and clinical signs associated with seropositivity in dogs. Am J Vet Res 2005;66:688–694.
14. Pappalardo BL, Brown TT, Tompkins M, et al. Immunopathology of Bartonella vinsonii (berkholzii) in experimentally infected dogs. Vet Immunol Immunopathol 2001;83:125–147.
15. Cherry NA, Jones SL, Maggi RG, et al. Bartonella spp. infection in healthy and sick horses and foals from the southeastern United States. J Vet Intern Med 2012;26:1408–1412.
16. Maggi RG, Moazzeni BR, Pultorak EL, et al. Bartonella spp. bacteremia and rheumatic symptoms in patients with Lyme disease-endemic region. Emerg Infect Dis 2012;18:783–791.
17. Lascelles BD, DePuy V, Thomson A, et al. Evaluation of a therapeutic diet for feline degenerative joint disease. J Vet Intern Med 2010;24:487–495.
18. Solano-Gallego L, Hegarty B, Espada Y, et al. Serological and molecular evidence of exposure to arthropod-borne organisms in cats from northeastern Spain. Vet Microbiol 2006;118:274–277.
19. Birrell F, Lunt M, Macfarlane G, et al. Association between pain in the hip region and radiographic changes of osteoarthritis: Results from a population-based study. Rheumatology (Oxford) 2005;44:337–341.
20. Peat G, Thomas E, Duncan R, et al. Estimating the probability of radiographic osteoarthritis in the older patient with knee pain. Arthritis Rheum 2007;57:794–802.

21. Popa C, Abdollahi-Roodsaz S, Joosten LA, et al. Bartonella quintana lipopolysaccharide is a natural antagonist of Toll-like receptor 4. Infect Immun 2007;75:4831–4837.

22. Pearce LK, Radecki SV, Brewer M, et al. Prevalence of Bartonella henselae antibodies in serum of cats with and without clinical signs of central nervous system disease. J Feline Med Surg 2006;8:315–320.

23. Breitschwerdt EB, Maggi RG, Chomel BB, et al. Bartonellosis: An emerging infectious disease of zoonotic importance to animals and human beings. J Vet Emerg Crit Care 2010;20:8–30.

24. Belgard S, Truyen U, Thibault JC, et al. Relevance of feline calicivirus, feline immunodeficiency virus, feline leukemia virus, feline herpesvirus and Bartonella henselae in cats with chronic gingivostomatitis. Berl Munch Tierarztl Wochenschr 2010;123:369–376.

25. Sykes JE, Westropp JL, Kasten RW, et al. Association between Bartonella species infection and disease in pet cats as determined using serology and culture. J Feline Med Surg 2010;12:631–636.

26. Fontenelle JP, Powell CC, Hill AE, et al. Prevalence of serum antibodies against Bartonella species in the serum of cats with or without uveitis. J Feline Med Surg 2008;10:41–46.

27. Perez C, Hummel JB, Keene BW, et al. Successful treatment of Bartonella henselae endocarditis in a cat. J Feline Med Surg 2010;12:483–486.

28. Varanat M, Travis A, Lee W, et al. Recurrent osteomyelitis in a cat due to infection with Bartonella vinsonii subsp. berkhoffii genotype II. J Vet Intern Med 2009;23:1273–1277.

29. Varanat M, Broadhurst J, Linder KE, et al. Identification of Bartonella henselae in 2 cats with pyogranulomatous myocarditis and diaphragmatic myositis. Vet Pathol 2012;49:608–611.

30. Abdollahi-Roodsaz S, Joosten LA, Roelofs MF, et al. Inhibition of Toll-like receptor 4 breaks the inflammatory loop in autoimmune destructive arthritis. Arthritis Rheum 2007;56:2957–2967.

31. Liu T, Gao YJ, Ji RR. Emerging role of Toll-like receptors in the control of pain and itch. Neurosci Bull 2012;28:131–144.

32. Christianson CA, Dumlao DS, Stokes JA, et al. Spinal TLR4 mediates the transition to a persistent mechanical hypersensitivity after the resolution of inflammation in serum-transferred arthritis. Pain 2011;152:2881–2891.

33. Jameson P, Greene C, Regnery R, et al. Prevalence of Bartonella henselae antibodies in pet cats throughout regions of North America. J Infect Dis 1995;172:1145–1149.

34. Breitschwerdt EB, Lappin MR. Feline bartonellosis: We’re just scratching the surface. J Feline Med Surg 2012;14:609–610.