Persistent Leptospiruria in Five Dogs Despite Antimicrobial Treatment (2000–2017)

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ABSTRACT

In dogs with leptospirosis, doxycycline therapy is recommended as the preferred therapy for its ability to eliminate the organism from all tissues, including the renal tubules. Elimination of organisms from the renal tubules terminates leptospiruria and prevents transmission of the organism. This report describes the discovery of persistent leptospiruria in the face of therapy with doxycycline in four dogs and enrofloxacin in one dog. Leptospiruria was confirmed by polymerase chain reaction testing for pathogenic leptospires in all five dogs. In two dogs, leptospiruria resolved after a change in therapy to enrofloxacin. In three dogs, doxycycline and/or enrofloxacin were ineffective at eliminating leptospiruria, which then resolved after therapy with clarithromycin. Pet owners could be at risk as persistent leptospiruria poses a potential zoonotic risk. The potential reasons for persistent leptospiruria as demonstrated by polymerase chain reaction testing are discussed. (J Am Anim Hosp Assoc 2019; 55:——–. DOI 10.5326/JAAHA-MS-6882)

Introduction

Leptospirosis is a global, water- and animal-borne zoonotic infectious disease caused by spirochetes in the genus *Leptospira* with evidence of endemic infections in wildlife and domestic reservoir animals.\(^1\)\(^–\)\(^4\) Epidemic infections in humans and dogs may occur in specific regions following flooding or anthropogenic activity that affects the habitat of wildlife, especially rodents.\(^1\)\(^–\)\(^4\) Infection with pathogenic leptospires can result in severe complications such as acute kidney injury, liver failure, and pulmonary hemorrhagic syndrome in both humans and dogs.\(^4\)\(^–\)\(^7\)

Given that leptospirosis is a bacterial infection, one would expect that treatment with appropriate antibiotics should shorten the course of disease, decrease mortality, and improve long-term outcomes. However, there are conflicting studies in humans assessing the value of antibiotic therapy in the treatment of leptospirosis, with some suggesting no survival benefit without addressing the reasons.\(^5\)\(^–\)\(^11\) It has been suggested that treatment in the late stages of disease may be an important factor that negatively impacts survival, or that immune-mediated mechanisms independent of clearance of the organism may play a more significant role in the pathology of the disease.\(^5\)\(^,\)\(^6\)

The lack of an obvious survival benefit in some studies may be influenced by factors unrelated to leptospirosis, however, as evidenced by a higher treatment failure in humans diagnosed with concurrent rickettsial and leptospirosis infections in Thailand.\(^12\) Despite no difference in survival benefit, Edwards et al. showed a reduction in leptospiruria with penicillin therapy as compared with no therapy, and Levett stated that the reduction in leptospiruria, regardless of the survival benefit, was justification alone for treatment.\(^5\)\(^,\)\(^8\) In addition to the reduction in leptospiruria, several studies have documented improved survival and reduced hospitalization with administration of appropriate antibiotic therapy early in the course of acute leptospirosis, justifying the World Health Organization’s recommendation for antibiotic treatment.\(^13\)\(^–\)\(^16\)

There are no studies in dogs comparing survival or outcome in dogs treated with antibiotics versus supportive care alone. However, both the European Consensus Statement and American College of Veterinary Internal Medicine Consensus Statement strongly recommended the use of doxycycline in dogs with leptospirosis.\(^6\)\(^,\)\(^7\) The recommendations were justified because of severe clinical manifestations of infection, including death, and the potential risk for
zoonotic transmission. Ampicillin is frequently the initial therapy for leptospirosis in dogs when oral doxycycline cannot be tolerated, but ampicillin does not eliminate leptospires from the kidney.5,6,17 Doxycycline has been shown to eliminate the organism from the kidney and effectively eliminate the risk of zoonotic transmission, which is why the European Consensus Statement and American College of Veterinary Internal Medicine Consensus Statement recommended initiating doxycycline therapy as early as oral medication would be tolerated.6,7,17

Persistent urinary shedding of spirochetes presumed to be leptospires, as determined by dark-field microscopy (both at presentation and 8 days after starting therapy), was reported in a single dog with acute renal failure and cholestatic liver disease, despite doxycycline therapy (10 mg/kg per os [PO] q 12 hr).18 Following the administration of streptomycin (15 mg/kg intramuscular q 12 hr for 3 days), dark-field microscopy was negative. In humans, persistence of urinary shedding as determined by polymerase chain reaction (PCR) testing was reported in six patients who had been treated with antibiotics (not specified) at the time of illness.19 Two of those PCR-positive results were confirmed by isolation of the leptospires on culture. To the authors’ knowledge, there are no studies in dogs that document either the duration of leptospiruria or persistent leptospiruria, as determined by PCR testing, in dogs who were treated with doxycycline.

In this case series, five dogs, four of whom (dogs 2–5) had disease consistent with acute leptospirosis, had persistent shedding of pathogenic leptospires, as confirmed by PCR testing of urine, despite antibiotic therapy. The results of PCR testing are chronicled in this case series. The results of serological testing by the microscopic agglutination test (MAT) are also reported4. For the sake of brevity, only creatinine is reported from the serum biochemistry. Renal failure was the sole disease associated with the positive PCR for pathogenic leptospires in all dogs in this report, none of the dogs had evidence of liver disease, and the results of the complete blood count were not significantly abnormal in any of the cases to warrant inclusion. Additional diagnostics to rule out other causes of renal failure, such as bacterial urine cultures and abdominal imaging performed on dogs 2–5, were also omitted for the sake of brevity. In addition, the details of supportive care, other than antibiotic therapy as indicated, were abbreviated as they did not provide information relevant to the focus of this case series.

Materials and Methods

Case 1

A 2 yr old, 11 kg, castrated male beagle presented to the Kansas State Veterinary Health Center (KSU-VHC) in January 2000, 5 days postcastration, for treatment of heartworm disease discovered during routine screening 2 wk prior, at which time the dog was clinically healthy apart from polyuria and polydipsia, and a urine specific gravity (USG) was 1.008 with 2+ proteinuria (no protein quantification was performed) and a serum creatinine was 1.8 mg/dL (reference interval 0.5–1.5 mg/dL). The dog had transferred ownership from a research colony in late December 1999 with no reports of related health problems.

At the time of evaluation (day 0) for treatment with melarsomine6, azotemia (creatinine 2.2 mg/dL; reference interval 0.5–1.5 mg/dL) was present. Urine was submitted for PCR testing for pathogenic leptospires and returned a positive result 2 days later. Treatment with doxycycline6 (9.2 mg/kg PO q 24 hr × 30 days) and prednisone4 (0.5 mg/kg PO q 12 hr × 7 days, followed by 0.5 mg/kg PO q 24 hr × 7 days, and then by 0.5 mg/kg q 24 hr every other day × 7 days) were instituted per recommendations of the American Heartworm Society as well as the recommended treatment for Leptospirosis.20

One month later (day 28), the dog presented for the second and third melarsomine injections. Azotemia was persistent (creatinine 1.9 mg/dL), and the USG was 1.009. A urine leptospirosis PCR assay was again positive. Serology by MAT revealed the highest reciprocal titer of 800 to serogroup Pomona (200 or less to all other serogroups). Doxycycline (9.2 mg/kg PO q 24 hr) was continued for an additional 2 wk.

Twenty-one days later (day 49), the dog was still azotemic (creatinine 1.9 mg/dL), and the MAT revealed a reciprocal titer to serogroup Pomona of 200, but all others were undetectable. Inadvertently, urine was not obtained, and doxycycline was discontinued. The dog was subsequently evaluated, but a urine PCR assay not performed, at 1, 1, 32, and 33 mo from that time point. At all four evaluations, the dog was reported to be clinically normal, and azotemia was persistent (creatinine 2.0, 1.9, 2.6, and 2.5 mg/dL, respectively). On the last examination (day 1059), a USG was 1.010 and urine PCR was positive. The dog was prescribed enrofloxacin6 (8 mg/kg PO q 12 hr × 3 wk).

One week after completing the course of enrofloxacin (day 1087), the dog was reported to be clinically normal, although azotemia was still present (creatinine 2.5 mg/dL). A PCR was negative for pathogenic leptospires. Over the next 6 mo, a PCR was performed on urine three more times (days 1147, 1189, 1220) and was negative each time. The creatinine was between 2.8 and 2.9 mg/dL on those three visits, and the dog was subsequently lost to follow-up.

Case 2

A 9 yr old, castrated male English bulldog presented to the KSU-VHC in September 2002 for lethargy and anorexia of 10 days duration, and polyuria and polydipsia, intermittent vomiting, and loose stool of
2 days duration. Physical examination was unremarkable, and the dog was azotemic (creatinine 6.3 mg/dL) with a USG of 1.012. Urine submitted for PCR was positive for leptospires. Serum submitted for MAT showed reciprocal titers of 12,800 to serogroups Pomona and Grippotyphosa and 100 or less to all other serogroups. The dog was hospitalized and treated with ampicillin\(^{1}\) (25 mg/kg IV q 8 hr) pending the PCR results (reported on day 4). Urine was submitted on day 5 for PCR and was reported positive for pathogenic leptospires on the same day. Creatinine was re-evaluated daily from day 2 to 7 of hospitalization and was 5.6, 3.5, 3.2, 3.5, 3.5, and 3.5 mg/dL, respectively. Urine was again submitted for PCR on day 7 of hospitalization and was reported positive on the same day. The dog was started on doxycycline (6.5 mg/kg PO q 12 hr) and was discharged because he was clinically stable.

The dog was re-evaluated 3, 10, 18, and 48 days following discharge. On each of these occasions, the PCR on urine was positive for leptospires, and the creatinine was 3.6, 3.0, and 2.5 on the first three visits, respectively, and was not performed on the last. Doxycycline was discontinued after the last evaluation, and enrofloxacin was started at 6 mg/kg PO q 12 hr for 2 wk.

The dog was re-evaluated the day after completion of enrofloxacin and was doing well clinically. Serum creatinine was 1.7 mg/dL and urine submitted for PCR was negative for leptospires. The dog was subsequently lost to follow-up.

**Case 3**

An 8 yr old, spayed female Pekingese presented to the KSU-VHC in July 2014 for evaluation of 2–3 days of lethargy, hyporexia, and azotemia (creatinine 9.0 mg/dL) documented that morning by the primary care veterinarian. Other than mild dehydration, the physical examination was unremarkable. Azotemia was confirmed (creatinine 8.8 mg/dL), and the USG was 1.009. Urine submitted for PCR was positive for pathogenic leptospires, and the MAT demonstrated reciprocal titers of 12,800 to serogroup Australis, 6400 to serogroup Pomona, 3200 to serogroup Grippotyphosa, and <100 to all other serogroups.

The dog was hospitalized and treated with ampicillin\(^{1}\)/sulbactam\(^{8}\) (22 mg/kg IV q 8 hr) and enrofloxacin (10 mg/kg IV q 24 hr). Serial creatinine measurements were performed over the following 6 days and were 9.0, 7.5, 6.3, 3.6, 3.0, and 3.3 mg/dL, respectively. The dog was discharged on day 9 with enrofloxacin (4.7 mg/kg PO q 24 hr) and amoxicillin/clavulanic acid\(^{6}\) (20 mg/kg PO q 12 hr).

The dog was re-evaluated on day 11, at which time the creatinine was 3.1 mg/dL, and the dog was reported to be doing well at home. On day 14, urine was collected and submitted for a PCR, which was positive for pathogenic leptospires. The previously prescribed antibiotics were discontinued, and doxycycline (10 mg/kg PO q 24 hr) was prescribed on day 17.

On day 29, the dog presented for a recheck examination. The dog was doing well at home and serum creatinine was 2.7 mg/dL. Urine was submitted for PCR and reported positive on day 34. On day 36, the serum creatinine was 2.2 mg/dL, doxycycline was discontinued, and the dog was started on clarithromycin\(^{1}\) (11 mg/kg PO q 12 hr).

The dog was presented on day 69 and was doing well at home. Serum creatinine was 1.9 mg/dL and urine submitted for PCR was negative for pathogenic leptospires. Clarithromycin was continued for 2 additional wk, and the dog was re-evaluated on day 130, at which time the creatinine was 2.1 mg/dL. Additional evaluations were performed on days 291, 539, and 688, at which time the creatinine was 2.0, 2.1, and 2.0, respectively. No additional PCR testing was performed.

**Case 4**

A 1 yr old, intact male bloodhound presented to KSU-VHC in September 2017 for treatment of leptospirosis. The dog was evaluated by a primary care veterinarian 12 days prior to presentation for fever and 5 wk of nonspecific, general malaise. The dog was reportedly mildly azotemic (values not reported), and an abdominal exploratory was performed but no abnormalities were identified. At that time, the dog was prescribed doxycycline\(^{2}\) (5 mg/kg PO q 12 hr), which was administered for 8 days. A urine sample obtained at the time of surgery was submitted for PCR for leptospirosis and reported positive 4 days prior to presentation, at which time the veterinarian discontinued doxycycline and began amoxicillin\(^{1}\) (22 mg/kg PO q 12 hr) and intravenous fluids (rate and type not specified). Bloodwork performed by the primary care veterinarian 3 days prior to presentation revealed a creatinine of 3.5 mg/dL, which climbed to 3.9 mg/dL on the morning prior to presentation to KSU-VHC.

Upon presentation to KSU-VHC, the physical examination was unremarkable. Urine submitted on day 1 for PCR was positive for pathogenic leptospires. The dog was hospitalized and treated with ampicillin\(^{1}/\)sulbactam\(^{8}\) (22 mg/kg IV q 8 hr) and enrofloxacin\(^{1}\) (10 mg/kg IV q 24 hr) pending the PCR results, which were reported on day 4. Creatinine was re-evaluated daily on days 2–6 of hospitalization and was 2.9, 2.9, 2.5, 2.5, 2.3 mg/dL, respectively. Urine was submitted on day 6 of hospitalization for PCR and was reported positive the next day. At this time (day 7), the previous antibiotics were discontinued, and the dog was started on clarithromycin\(^{1}\) (9.6 mg/kg PO q 12 hr). Urine submitted for PCR on day 8 was reported positive 3 days after the patient was discharged (day 11) because of significant clinical improvement.

The dog was re-evaluated on day 13, and the urine PCR for leptospirosis was negative and creatinine was 2.2 mg/dL. The dog was
prescribed an additional 2 wk of clarithromycin at 9.6 mg/kg PO q 12 hr, and the dog was subsequently lost to follow-up.

Case 5

A 3 yr old, castrated male toy poodle mix presented to KSU-VHC in October 2017 for evaluation of polyuria and polydipsia of 2–3 wk duration and inappetence of 1 wk duration. The dog was evaluated by a primary care veterinarian 7 days prior to presentation, at which time a USG was 1.007 and serum was collected for MAT testing. The dog was discharged on amoxicillin/clavulanic acid6 (11.4 mg/kg PO q 12 hr). The MAT was reported 2 days prior to presentation and revealed a reciprocal titer to serogroup Grippotyphosa of >6400. Bloodwork performed 1 day prior to presentation to KSU-VHC revealed a creatinine of 3.7 mg/dL.

Upon presentation to KSU-VHC, physical examination revealed mild dehydration. Urine was collected and submitted for a leptospirosis PCR. The dog was hospitalized and treated with enrofloxacin⁷ (6.2 mg/kg PO q 12 hr) pending the PCR results (reported positive on day 2). Creatinine was re-evaluated on days 1 and 2 (2.2 and 1.7 mg/dL, respectively). Urine was submitted for a PCR on day 3 and was reported positive the following day. The dog was discharged with enrofloxacin (6.2 mg/kg PO q 12 hr) on day 3 after clinical improvement.

On day 10, the creatinine was 2.6 mg/dL, and leptospirosis PCR on urine was positive. Enrofloxacin was discontinued, and the dog was started on clarithromycin⁸ (10.9 mg/kg PO q 12 hr) for 3 wk. An additional PCR performed on urine on day 22 was negative. No additional follow-up was available.

Discussion

This case series presents five dogs who remained positive for pathogenic leptospires by PCR despite following the recommended treatment with either an initial beta lactam or doxycycline.⁶,⁷ In three of the dogs (cases 1–3), the course of doxycycline therapy met or exceeded the recommended minimum duration of 3 wk, at which time all three dogs were still positive by PCR. Case 4 received 8 days of doxycycline, after which the PCR was still positive. One dog (case 5) never received doxycycline but was initially treated with amoxicillin/clavulanic acid. Two dogs (cases 1 and 2) were subsequently treated with enrofloxacin, after which a negative PCR was obtained. Enrofloxacin was apparently ineffective in clearing leptospiruria in cases 3–5, who required therapy with clarithromycin. In each of these dogs, the persistence of leptospiuria represented a potential zoonotic risk to pet owners and veterinary personnel, a consideration that may be overlooked by all at-risk groups after the initiation of therapy (specifically doxycycline) that is expected to resolve leptospiuria.

Whether the documented persistent leptospiuria represents antibiotic resistance on the part of the infecting leptospires or a patient-specific problem related to oral absorption of the antibiotics and failure to achieve therapeutic drug concentrations is not known. The potential for antibiotic resistance in pathogenic leptospires represents a relatively unexplored concern in leptospirosis research but could have a major impact on disease treatment and control if present.

The authors are unaware of any placebo-controlled studies evaluating the efficacy of antimicrobial agents for the treatment of leptospirosis in dogs. However, a number of studies have evaluated the efficacy of a variety of antibiotics compared with placebo in hamsters.¹⁷–²⁴ In these studies, the mortality rate of untreated hamsters was 100%, whereas the survival rate was at or near 100% with many of the antimicrobials with which the hamsters were treated, including doxycycline, fluoroquinolones, and first-generation cephalosporins. Several studies have investigated the use of alternatives to penicillin G or doxycycline in the treatment of humans with leptospirosis and determined that azithromycin, cefotaxime, and ceftriaxone were as effective.¹²,²⁵,²⁶

Several in vitro studies have evaluated antimicrobial susceptibilities of pathogenic Leptospira isolates using a broth microdilution protocol and determined that many antimicrobial agents demonstrate minimum inhibitory concentrations (MIC) in the range that would support their use in clinical patients, including ampicillin, cefepime, azithromycin, clarithromycin, cefotaxime, ceftriaxone, doxycycline, erythromycin, and ciprofloxacin.²⁷–²⁹ Although doxycycline is considered to be the preferred drug for treating leptospirosis, all three studies reported Leptospira isolates with an MIC to doxycycline far above the other isolates, including 1 of 46 (Chakraborty et al.), 3 of 26 (Murray et al.), and 5 of 13 isolates (Ressner et al.).²⁷–²⁹ Both Ressner et al. and Suepal et al. reported higher MICs to doxycycline among Leptospira isolates in various geographical regions of the world and suggested that frequent and unregulated use of doxycycline for various endemic diseases may be responsible for decreased susceptibility.²⁸,³⁰

The authors are unaware of any study in any species that has evaluated the persistence of urinary shedding of leptospires during or after treatment as a function of achieved or achievable concentrations of antibiotics in the kidney or urine. It is reasonable to presume that one reason these dogs failed to resolve leptospiuria was poor oral absorption of doxycycline. Urine concentration of doxycycline was not measured in any of the dogs, unfortunately, to confirm or refute this hypothesis. Poor oral absorption would not explain the lack of response to enrofloxacin in dog 3, however, as enrofloxacin was administered intravenously during the initial stages of the disease.

The argument could be made that the persistent PCR results in these dogs were a function of detecting deoxyribonucleic acid from...
nonviable or effete leptospires and not predictive of active infection. Although that possibility exists, rapid clearance of leptospires has been documented in as little as 2–3 days in a Syrian hamster model. In hamsters treated with doxycycline (10 mg/kg once), leptospires were cleared in all target organs (including kidneys and liver) as determined by PCR within 3 days, suggesting that nonviable leptospires are cleared rapidly from target organs. In another hamster model evaluating the efficacy of cefepime, ertapenem, and norfloxacin, PCR results had a high correlation with culture results, also supporting the idea that residual, nonviable genetic material is an unlikely cause of persistent PCR results. Culture for leptospirosis was not performed on any of the dogs in the current case study, but extrapolating the results from studies on other species, one would expect that when given the correct antimicrobial therapy, a dog should experience rapid clearance of leptospires from the urine. Further studies are needed to better determine the specific time period required for complete clearance to be achieved in dogs, but the findings in the hamster models support the concern that a persistent positive PCR result is consistent with active infection and a continued zoonotic risk, even in a clinically improved dog.

Because cultures specific for leptospirosis were not performed on any of the dogs in this study, it cannot be ascertained whether these dogs were infected with a serovar or strain that is unique to this geographic area and possessing antibiotic-resistance genes that are not seen in the most common serovars that infect dogs. Ressner et al. raised the possibility of geographic variability in susceptibility to antimicrobial agents; in their study, however, variability was identified in globally distinct regions. Infection with lesser-seen serovars or strains could provide a potential explanation for the suspected resistance to routine antimicrobial therapy for leptospirosis. For each of the cases presented in this series, the authors did determine that they were from the immediate referral region surrounding the KSU-VHC. In 2016, Harkin et al. reported that the majority (80%) of all leptospiral deoxyribonucleic acid isolated from canine urine samples from the continental United States were from Leptospira kirschneri serovar Grippotyphosa strain DE. From the combined Kansas, Nebraska, and South Dakota region, 46 isolates were identified as Grippotyphosa DE, and 3 isolates were unidentified. Although it seems most likely that these dogs would have been infected with the more common isolate, an atypical leptospirosis serovar infection with unique antimicrobial susceptibility remains a possibility.

There are additional considerations about several of these cases. In dog 1, there were no records of prior laboratory work to document normal kidney function prior to the first evaluation at KSU-VHC. The azotemia in that dog may have reflected glomerulonephritis as a consequence of heartworm infestation and not leptospirosis. Regardless of whether leptospirosis contributed to the azotemia, the dog was actively shedding pathogenic leptospires in the urine after initiating doxycycline therapy. The lapse in PCR testing that spanned more than 32 mo was a reflection of an assumption by the veterinarian primarily overseeing the case that leptospirosis would be cleared by doxycycline and that no additional testing was required. Although the last positive PCR could reflect repeat infection, the possibility that it reflects persistent leptospirosis in a dog for nearly 3 yr has significant public health ramifications. Although reinfection has never been documented in the veterinary literature, and natural immunity to the infective serovar is expected for several months following natural infection, it does remain a possibility in these cases and explanation for persistently positive PCR results.

In the remaining cases (dogs 2–5), acute renal failure was convincingly present to the veterinarian of record in each case, and to both authors, based on a review of all available medical records. The slow resolution of azotemia and eventual termination of leptospirosis in these dogs could reflect the natural disease course that leptospirosis was going to take in these individuals, regardless of specific antibiotic therapy, as has been shown in humans. It is also possible that some of these dogs developed chronic kidney disease as a consequence of immune-mediated mechanisms unrelated to the presence of leptospires in the kidneys. The authors speculate that failure to achieve a creatinine within reference intervals could also reflect administration of an antibiotic to which the leptospires are resistant, resulting in a longer duration of infection and more prolonged nephritis from the dog’s innate immune response, and that this immune-mediated nephritis might be minimized with the appropriate antibiotic.

For dog 4, enrofloxacin was started at KSU-VHC as the dog had already received doxycycline and showed no apparent improvement, although admittedly, the dog was not hospitalized for fluid therapy during those 8 days of doxycycline. Dog 5 never received doxycycline, so it cannot be stated that doxycycline would have been ineffective, but enrofloxacin appeared to be ineffective in resolving leptospirosis.

An additional consideration is the variety in antimicrobial regimens. Given the retrospective nature of this case series, and the involvement of multiple clinicians, a consistent protocol for antimicrobial administration and duration was unable to be established. Despite the variability, the evidence and suggestion for persistently infected dogs with leptospirosis still remains and constitutes discussion.

**Conclusion**

This case study documents five dogs who remained positive on PCR for pathogenic leptospires in the urine despite following the recommended treatment protocol. The role that persistent leptospirosis...
played in the persistence of an elevated creatinine in these dogs is unknown but warrants investigation in other dogs with leptospirosis. The reason for persistent leptospiuria was not determined in these dogs, but the clinically relevant finding is that leptospiuria can be persistent in the face of doxycycline therapy, as well as various other antimicrobials, and presents a potential for zoonotic transmission of the organism. The authors propose that performing a PCR for pathogenic leptospires on urine after 7 days of therapy, prior to the end of the recommended 2 wk course of doxycycline therapy, to confirm that leptospiuria has been eliminated would be beneficial given available evidence.

FOOTNOTES

a Kansas State Veterinary Diagnostic Laboratory, Manhattan, Kansas
b Immixide; Merial, Merial Caribbean, West Indies
c Doxycycline; Pfizer, Pfizer Inc, New York, New York
d Prednisone; Roxane Laboratories Inc, Columbus, Ohio
e Baytril; Bayer, Shawnee Mission, Kansas
f Ampicillin; Sandoz Inc, Princeton, New Jersey
g Unasyn; Roerig, Pfizer Inc, New York, New York
h Clavamox; Zoetis Inc, Kalamazoo, Michigan
i Clarithromycin; Sandoz Inc, Princeton, New Jersey
j Amoxicillin; Pfizer Inc, New York, New York
k Cefdinir; Abbott Laboratories, North Chicago, Illinois

REFERENCES
