

Comparison of the efficacy of amoxicillin-clavulanic acid, cefovecin, and doxycycline in the treatment of upper respiratory tract disease in cats housed in an animal shelter

Annette L. Litster, BVSc, PhD, MMedSci; Ching Ching Wu, DVM, PhD; Peter D. Constable, BVSc, PhD, DACVIM

Objective—To compare efficacy of amoxicillin-clavulanic acid, cefovecin, and doxycycline in shelter-housed cats with clinical signs of upper respiratory tract disease (URTD).

Design—Randomized prospective clinical trial.

Animals—48 cats with URTD.

Procedures—Conjunctival and nasal swab specimens were obtained for culture and susceptibility testing, and cats were randomly assigned to 3 treatment groups (16 cats/group) on day 1: amoxicillin-clavulanic acid (12.5 mg/kg [5.68 mg/lb], PO, q 12 h, for 14 days), cefovecin (8.0 mg/kg [3.64 mg/lb], SC, once), or doxycycline (10.0 mg/kg [4.55 mg/lb], PO, q 24 h, for 14 days). Oculonasal discharge, sneezing, coughing, dyspnea, demeanor, and food intake were scored twice daily for 14 days (scale, 0 [subjectively normal] to 3 [markedly abnormal]).

Results—The most common bacterial isolates were *Mycoplasma* spp (n = 22) and *Bordetella bronchiseptica* (9). Cats treated with amoxicillin-clavulanic acid or doxycycline had significantly increased body weight by day 14. Cats that received doxycycline had significantly lower overall oculonasal discharge scores than those treated with amoxicillin-clavulanic acid or cefovecin. Cats treated with amoxicillin-clavulanic acid or doxycycline had significantly lower overall sneezing scores than those that received cefovecin. Cats that received amoxicillin-clavulanic acid had significantly decreased demeanor and food intake scores on day 2, whereas this was detected later in other groups (demeanor score on days 5 and 7 and food intake score on days 10 and 11 in the cefovecin and doxycycline groups, respectively).

Conclusions and Clinical Relevance—Oral administration of amoxicillin-clavulanic acid or doxycycline appeared to be more effective than a single SC injection of cefovecin in treating cats with clinical signs of URTD. (*J Am Vet Med Assoc* 2012;241:218–226)

Upper respiratory tract (ie, nasal cavity, nasopharynx, and trachea) disease in cats is among the most common causes of euthanasia in animal shelters¹ and represents a serious challenge to veterinarians managing the health of cats housed in animal shelters. The combination of stress associated with relocation to a shelter, presence of large numbers of cats in potentially crowded conditions, and variability in immune status increases morbidity and mortality rates attributed to URTD in shelter cats.² The risk of disease transmission through the population, difficulties and cost of caring for infected cats, and problem of potentially reduced adoptability may result in euthanasia in a shelter situation, even though URTD in cats in a home environment is usually manageable.¹

ABBREVIATIONS

BW	Body weight
FCV	Feline calicivirus
FHV	Feline herpesvirus
LSM	Least squares mean
MIC ₉₀	Minimal concentration to inhibit 90% of bacterial growth
URTD	Upper respiratory tract disease

Mycoplasma spp, *Chlamydomydia felis*, *Bordetella bronchiseptica*, FHV, and FCV were isolated from cats with URTD in a California shelter-based study.¹ The isolation of FCV, *Mycoplasma* spp, and *C felis* was significantly associated with clinical signs of URTD in that study,¹ including conjunctivitis, ocular or nasal discharge, gingivitis, and oral vesicles. Four other studies^{3–6} have yielded statistical evidence of an association between clinical signs of URTD and the presence of FHV, FCV, *Mycoplasma* spp, *C felis*, and *B bronchiseptica*, and investigators of 1 study⁷ reported more severe clinical signs in cats infected with multiple pathogens. Cats that appear to be clinically recovered from URTD may remain persistently infected⁸ and serve as sources of infectious agents in the shelter. Whereas primary vi-

From the Departments of Veterinary Clinical Sciences (Litster, Constable) and Comparative Pathobiology (Wu), College of Veterinary Medicine, Purdue University, West Lafayette, IN 47907.

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Address correspondence to Dr. Litster (catvet@purdue.edu).

ral infections with FHV and FCV are prevalent in cats with URTD,¹ secondary bacterial invasion by *Pasteurella* spp, *Escherichia coli*, *Staphylococcus* spp, *Streptococcus* spp, or *Micrococcus* spp regularly develops.^{5,7,9,10} Fluoroquinolones, β -lactams, tetracyclines, and broad-spectrum macrolide antimicrobials (eg, azithromycin) have therefore been used as part of the treatment of cats with suspected bacterial URTD.¹¹ Amoxicillin-clavulanic acid is effective in vitro against *C felis*,¹² *B bronchiseptica*,¹³ *Staphylococcus* spp, and *Streptococcus* spp but is less effective in vitro against most gram-negative isolates.⁹ Doxycycline is reported to be effective in vitro against *Mycoplasma* spp,¹⁴ *C felis*,¹⁵ and *B bronchiseptica*¹⁶ and is efficacious for the treatment of *Pasteurella* spp infections.⁹ However, the results of a recent study⁹ of in vitro antimicrobial susceptibility of bacterial isolates cultured from respiratory samples from cats with respiratory tract disease indicated that the overall efficacy of doxycycline was relatively poor.

Cefovecin is a semisynthetic third-generation cephalosporin with bactericidal activity against both gram-positive and gram-negative pathogens.¹⁷ It is formulated as an aqueous solution and is rapidly absorbed in cats after SC injection.¹⁸ After absorption, cefovecin is slowly eliminated and produces long-lasting circulating concentrations of unbound drug in extracellular fluid that permits a 14-day dosing interval.¹⁸ Cefovecin's prolonged effective plasma concentrations and SC route of administration facilitate compliance and could avoid potential stress associated with repeated oral administration of antimicrobials in cats.¹⁸ Although cefovecin has in vivo clinical efficacy for the treatment of skin¹⁹ and lower urinary tract infections²⁰ in cats, to the authors' knowledge, cefovecin has not been clinically assessed for use as part of the treatment regimen for URTD in cats. However, in a large study⁹ of feline bacterial respiratory infections, cephalexin (a second-generation cephalosporin) was ranked second only to enrofloxacin for in vitro efficacy against the most frequently isolated bacterial species. *Bordetella*, *Mycoplasma*, and *Chlamydophila* spp were not among the most frequently isolated bacterial species in the population examined in that study,⁹ thus explaining this unexpected finding because cephalexin is not expected to be an effective treatment for these infections. The main objective of the study reported here was to compare the efficacy of amoxicillin-clavulanic acid, cefovecin, and doxycycline in shelter-housed cats with clinical signs of URTD.

Materials and Methods

Animals—Forty-eight adult cats admitted to a large (annual intake, > 1,500 cats) private animal shelter in Chicago between April 6, 2009, and January 27, 2010, were enrolled in the study. The selection criterion for the study was clinical signs of URTD as assessed during physical examination by a veterinarian \leq 24 hours after admission into the shelter. There were no specific exclusion criteria at enrollment. All cats had previously been transferred from a large municipal shelter where they had been admitted as strays or surrendered by their owners \geq 5 days before admission to the private shelter where the study was performed. At the municipal shelter, cats were vaccinated only at the time of intake

with a combination modified-live feline panleukopenia, calicivirus, and herpesvirus vaccine^a administered SC. This vaccination^a was repeated, and serologic tests were performed for anti-FIV antibodies and FeLV antigen^b at the time of intake into the private shelter.

Conjunctival and nasal samples were collected from each cat with swabs^c at enrollment (\leq 24 hours after admission into the private shelter; study day 1 for each cat) and stored at -80°C until submission for microbiological testing at the Indiana Animal Disease Diagnostic Laboratory.

After specimen collection, a randomized block method was used to allocate cats to 3 antimicrobial treatment groups: amoxicillin-clavulanic acid, cefovecin, or doxycycline, with 16 cats/group. The randomization sequence was created by use of randomization software^d with a fixed block size of 16 in each treatment group. The initial randomization scheme consisted of the amoxicillin-clavulanic acid and cefovecin arms and was used for the first 22 cats (from April 6 to August 26, 2009; amoxicillin-clavulanic acid group [n = 12]; cefovecin group [10]). Because doxycycline is commonly used in shelters for the treatment of URTD in cats, the decision was made to include a third doxycycline arm but to preserve the original study design of equal numbers of cats randomly assigned to each treatment group. For the remaining 26 cats in the study (enrolled between October 15, 2009, and January 27, 2010), the same randomization software was used to allocate 4 cats into the amoxicillin-clavulanic acid group, 6 cats into the cefovecin group, and 16 cats into the doxycycline group. Amoxicillin-clavulanic acid and doxycycline were chosen because they had been commonly used by veterinarians at the private shelter to treat URTD in cats in the past, and cefovecin was chosen because of its convenient dose administration protocol. Cats were removed from the study and another antimicrobial was prescribed if, in the opinion of the attending shelter veterinarian, there was insufficient clinical response to the allocated antimicrobial treatment after 4 to 7 days of treatment.

Cats in the amoxicillin-clavulanic acid group received amoxicillin-clavulanic acid^e (12.5 mg/kg [5.68 mg/lb], PO, q 12 h) for 14 days; this dosage protocol was selected on the basis of previously reported in vivo efficacy¹¹ and results of a pharmacokinetic study²¹ of the drug in this species. Cats in the cefovecin group received 1 dose of cefovecin^f (8.0 mg/kg [3.64 mg/lb], SC), and those in the doxycycline group received doxycycline^g dissolved in a solubilizing agent containing B-complex vitamins^h (10.0 mg/kg [4.55 mg/lb], q 24 h) for 14 days. The dosage protocols for cefovecin and doxycycline were selected on the basis of pharmacokinetic studies^{18,22} in cats. Treatments were administered by veterinary technicians employed at the shelter. Cat housing at the private animal shelter consisted of a bank of 9 solid-sided stainless steel cages in 1 room, with each cage measuring 24 \times 24 \times 24 inches. Each cage contained soft bedding (a towel or similar item), food, water, and a litter tray but no toys or structures in which to hide.

The study endpoint for each cat occurred at the end of the 14-day study period or at the time it received different antimicrobial drugs in addition to, or instead

of, the allocated treatment. Follow-up health evaluations were performed by the attending shelter veterinarian weekly until each cat was adopted. The study protocol was approved by the Purdue Animal Care and Use Committee.

Evaluation of clinical signs of URTD—A scoring system was used to assess clinical signs of URTD (Appendix). Scoring was initially performed by a veterinarian masked to treatment group on the day of admission, immediately before treatment group allocation. Veterinary technicians who were aware of treatment group allocation were trained to use the scoring system and performed scoring twice daily for the following 13 days. One investigator (ALL) trained the staff by explaining the scoring system using enrolled cats as examples on the day of enrollment of the first 9 cats and followed up initial training by spot-checking the scores during the study. Twice-daily oral examinations for ulcerations were also conducted. Veterinary technicians performing scoring had access to the observations from the previous day. Use of topical ophthalmic antimicrobials was recorded and constituted the study endpoint for ocular discharge score only.

Cats were fed a mixture of commercially available canned and dry cat foodⁱ each morning and evening. Dry food was fed in a quantity sufficient to be considered ad libitum, and extra canned food was offered to cats that appeared to have a preference for it. Dietary alternatives were available for cats that did not eat well, and these were selected by technicians responsible for feeding the cats, in consultation with shelter veterinarians. Food intake observations for each feeding were made at the following feeding time (ie, approx 12 hours later). Cats were weighed at intake and on study days 7 and 14.

Laboratory analysis—One set of conjunctival and nasal swabs was tested by means of routine aerobic culture protocols.²³ Briefly, swabs were streaked onto 5% sheep blood agar plates and MacConkey agar plates and incubated at $35 \pm 1^\circ\text{C}$ with 5% CO_2 for 24 to 48 hours. Colonies that were suspected to be common respiratory pathogens such as *B bronchiseptica*, *Pasteurella multocida*, and *Streptococcus* spp were evaluated by use of an automatic identification system^l and antimicrobial susceptibility testing.^k Minimum inhibitory concentrations for commonly used antimicrobials were determined via broth microdilution assay as previously described.²⁴

A second set of swabs was used for *Mycoplasma* spp culture. The swabs were placed in 3 mL of *Mycoplasma* culture medium,^l and serial 10-fold dilutions (10^{-1} to 10^{-6}) were prepared and incubated at $35 \pm 1^\circ\text{C}$ with 5% CO_2 for 1 month. All tubes of inoculated media were examined weekly for color change. Those with color change were subjected to standard fluorescent antibody assay^m confirmation by use of specific anti-*Mycoplasma* antibodies.ⁿ

Statistical analysis—Data are expressed as LSM \pm SE. Values of $P < 0.05$ were regarded as significant for all tests except for the described use of Bonferroni-adjusted P values. A Fisher exact test^o was used to compare the numbers of spayed and sexually intact females and castrated and sexually intact males in each group.

Analysis of variance^p was used to evaluate differences in the following variables among groups: age, rectal temperature on admission, days of study participation, and total days to approval for adoption (determined on the basis of results of physical examination by a veterinarian). Age and days to approval for adoption were log transformed before ANOVA was performed to stabilize variances.

Repeated-measures ANOVA^q was used to evaluate the main effects of treatment, time, and the interaction between treatment and time by use of an autoregressive covariance structure. Score data were globally ranked (rank transform procedure) before applying repeated-measures ANOVA.²⁵ The global ranking method was selected because it increases statistical power while providing a robust analytic method in the presence of heterogeneous variance and skewed distributions when sample sizes are equal.^{25,26} When indicated by significant results of an F test for time, LSM ranked score values were compared with those recorded for the first study day by use of Bonferroni-adjusted P values (resulting in $P < 0.0079$ being significant for this within-group comparison). This post hoc analysis was used to determine the first day when clinical scores were significantly different from scores on study day 1. Between-group comparisons at each time point were not made (except for the first study day) because of the large number of comparisons.

The P value for the main effect of treatment or the interaction between treatment and time identified by the rank transform procedure was compared with that obtained via stratified categorical analysis controlling for the effect of time via a Friedman χ^2 test.^r

Results

Animals—Cats ranged in age from 6 months to 7.5 years (median, 1 year; upper quartile, 1.75 years; lower quartile, 0.9 years). There were 17 sexually intact females, 6 spayed females, 16 sexually intact males, and 9 neutered males. Results of serologic assays for FeLV antigen and anti-FIV antibodies were negative for all cats. There was no difference in age (F test, $P = 0.90$; overall LSM, 1.7 ± 0.2 years), rectal temperature on admission ($P = 0.35$; overall LSM, $39.1 \pm 0.2^\circ\text{C}$ [$102.4 \pm 0.3^\circ\text{F}$]), or the number of spayed or sexually intact females and castrated or sexually intact males ($P = 0.76$) among groups (data not shown). Clinical scores were similar for all 3 groups on study day 1 (Figures 1–4). Although nonsignificant ($P = 0.065$), demeanor score appeared to be higher in cats in the cefovecin group (1.00 ± 0.14) than in the amoxicillin-clavulanic acid (0.81 ± 0.14) and doxycycline (0.88 ± 0.14) groups on day 1. Overall scores for demeanor were 0.90 ± 0.08 on day 1 and 0.08 ± 0.09 on day 14, and overall scores for food intake were 1.15 ± 0.13 on day 1 and 0.27 ± 0.15 on day 14. The only adverse drug-related events observed during the study were mild transient pain on injection (duration, < 30 seconds) in 2 cats in the cefovecin group.

Three cats were removed from the amoxicillin-clavulanic acid group on days 3, 7, and 9; 1 cat was removed from the cefovecin group on day 6, and another 2 cats were removed this group on day 8; and 3 cats were removed from the doxycycline group on days 4, 6,

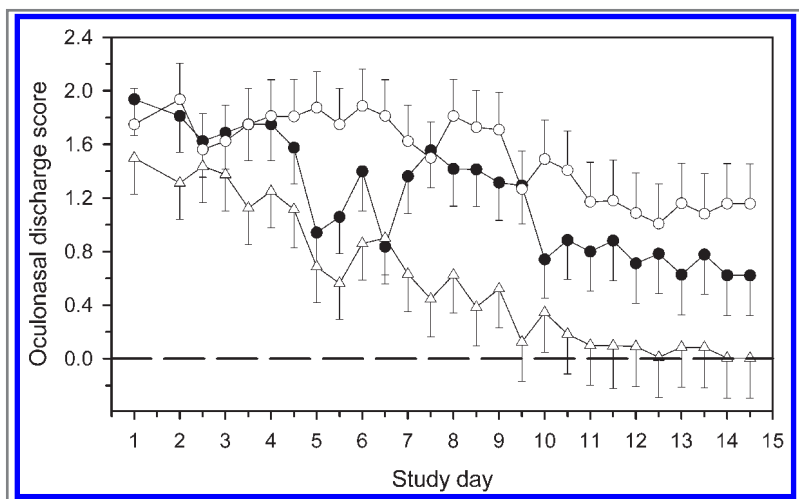


Figure 1—Least squares mean \pm SE oculonasal discharge scores (range of possible scores, 0 [subjectively normal] to 3 [markedly abnormal]) in shelter-housed cats with clinical signs of URTD on the day of shelter intake (day 1) and for the subsequent 14 days. Cats were randomly assigned to 3 treatment groups ($n = 16/\text{group}$) immediately after the oculonasal discharge score was recorded on day 1: amoxicillin-clavulanic acid (12.5 mg/kg [5.68 mg/lb], PO, q 12 h, for 14 days; black circles), cefovecin (8.0 mg/kg [3.64 mg/lb], SC, once; white circles), or doxycycline (10.0 mg/kg [4.55 mg/lb], PO, q 24 h, for 14 days; white triangles). Clinical evaluations were performed twice daily after day 1. Between days 3 and 9, 9 cats (3/treatment group) were removed from the study when the choice of antimicrobial was changed because of apparent treatment failure.

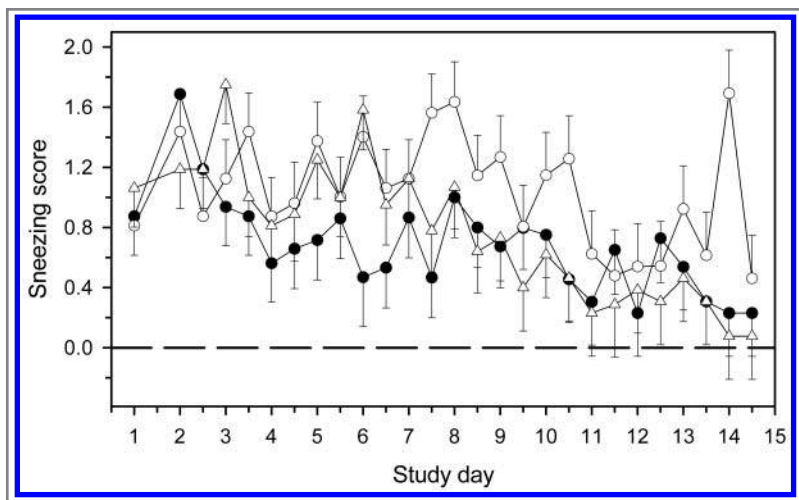


Figure 2—Least squares mean \pm SE sneezing scores in shelter-housed cats treated for clinical signs of URTD with amoxicillin-clavulanic acid, cefovecin, or doxycycline. See Figure 1 for key.

and 7. All 9 of these cats were removed from the study because a decision was made by the attending shelter veterinarian to change the antimicrobial prescribed on the basis of physical examination findings that indicated treatment failure. Alternative treatments included enrofloxacin (5 mg/kg [2.3 mg/lb], PO, q 24 h) or one of the other study drugs at previously described doses for 5 to 7 days after removal from the study. In the amoxicillin-clavulanic acid group, 2 of the 3 cats received doxycycline and the remaining cat received enrofloxacin. In the doxycycline group, 2 of the 3 cats received enrofloxacin, and the remaining cat received amoxicillin-clavulanic acid. In the cefovecin group, 2 cats received enrofloxacin, and 1 cat received amoxicillin-clavulanic acid. Alternative treatments were successful in all 9 cats. There was

no difference between treatment groups in the number of days of study participation (F test, $P = 0.95$; overall LSM, 11.8 ± 0.4 days) or number of days from intake to being deemed suitable for adoption ($P = 0.55$, overall LSM, 25.5 ± 2.4 days) on the basis of physical examination findings. All cats remaining in the study were included in the statistical analysis conducted on each study day (39 to 48 cats, depending on the study day).

Microbiological assays—*Mycoplasma* spp were the most common isolates cultured from both conjunctival and nasal swabs, but *Staphylococcus epidermidis* was also cultured from both of these sites. *Mycoplasma* spp were isolated from 22 of 48 (46%) cats; these included cats in the amoxicillin-clavulanic acid ($n = 8$), cefovecin (9), and doxycycline groups (5). Both conjunctival and nasal swabs yielded *Mycoplasma* spp in 11 cats (amoxicillin-clavulanic acid group [$n = 5$] and cefovecin group [6]); *Mycoplasma* spp were isolated only from conjunctival swabs of 5 cats (cefovecin group [$n = 1$] and doxycycline group [4]) and only from nasal swabs of 6 (amoxicillin-clavulanic acid group [3], cefovecin group [2], and doxycycline group [1]). *Bordetella bronchiseptica* was cultured only from nasal swabs (9 [19%] cats; 3 in the amoxicillin-clavulanic acid group and 6 in the doxycycline group), as were group G β -hemolytic *Streptococcus* spp (2 [4%]; 1 each in the amoxicillin-clavulanic acid and cefovecin groups). *Staphylococcus epidermidis* was isolated from conjunctival swabs in 3 (6%) cats (amoxicillin-clavulanic acid group [2] and doxycycline group [1]) and from nasal swabs in 2 (4%; both in the doxycycline group). *Staphylococcus aureus* subsp *aureus* was cultured from the nasal swab of 1 cat in the doxycycline group. Results of antimicrobial susceptibility testing indicated that all 9 *B bronchiseptica* isolates were susceptible to amoxicillin-clavulanic acid ($\text{MIC}_{90} \leq 4 \mu\text{g/mL}$) and doxycycline ($\text{MIC}_{90} \leq 2 \mu\text{g/mL}$) but resistant to cefovecin ($\text{MIC}_{90} > 8 \mu\text{g/mL}$). All *Staphylococcus* spp and *Streptococcus* spp isolates cultured appeared to be susceptible to all 3 antimicrobials (amoxicillin-clavulanic acid, $\text{MIC}_{90} \leq 4 \mu\text{g/mL}$; cefovecin, $\text{MIC}_{90} \leq 0.25 \mu\text{g/mL}$; and doxycycline, $\text{MIC}_{90} \leq 2 \mu\text{g/mL}$). Antimicrobial susceptibility testing was not performed for *Mycoplasma* isolates.

Clinical response—Among cats ≥ 1 year old (amoxicillin-clavulanic acid group [$n = 9$], cefovecin group [12], and doxycycline group [10]), BW was significantly increased in the amoxicillin-clavulanic acid and doxycycline groups on day 14, compared with the value on day 1; however, only in the amoxicillin-clavulanic acid group

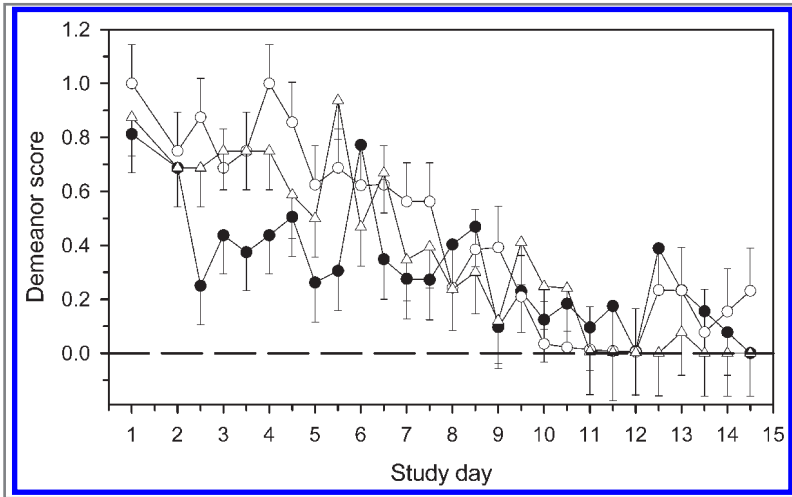


Figure 3—Least squares mean \pm SE demeanor scores in shelter-housed cats treated for clinical signs of URTD with amoxicillin-clavulanic acid, cefovecin, or doxycycline. See Figure 1 for key.

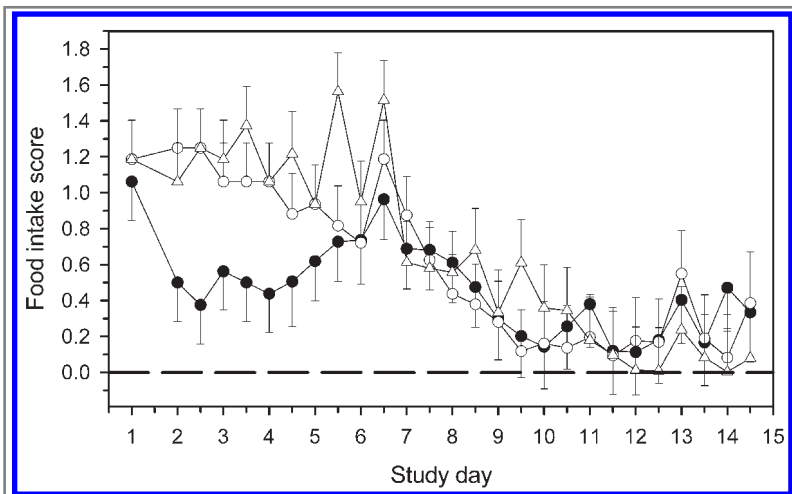


Figure 4—Least squares mean \pm SE food intake scores in shelter-housed cats treated for clinical signs of URTD with amoxicillin-clavulanic acid, cefovecin, or doxycycline. See Figure 1 for key.

was BW increased on day 7 (Table 1). There was a significant effect of treatment on oculonasal discharge score (Figure 1). Cats treated with doxycycline had significantly lower oculonasal discharge scores (LSM, 0.59 ± 0.15) than did cats treated with amoxicillin-clavulanic acid (1.19 ± 0.15 ; $P = 0.002$) or cefovecin (1.52 ± 0.15 ; $P < 0.001$). There was no difference ($P = 0.11$) in oculonasal discharge score between the amoxicillin-clavulanic acid and cefovecin groups. The first day that oculonasal discharge score was significantly decreased, compared with the day 1 value, was day 9 in the doxycycline group and day 10 in the amoxicillin-clavulanic acid group. Changes in oculonasal discharge score in the cefovecin group throughout the 14-day study period were not significant.

There was a significant effect of treatment on sneezing score (Table 1; Figure 2). Cats treated with amoxicillin-clavulanic acid or doxycycline had significantly lower sneezing scores (LSM, 0.68 ± 0.08 ; $P = 0.003$ and 0.76 ± 0.08 ; $P = 0.015$, respectively) than did cats treated with cefovecin (1.04 ± 0.08). Sneezing scores were not significantly ($P = 0.54$) different between the amoxicillin-clavulanic acid and doxycycline groups. Sneezing scores did not change significantly in any of the 3 individual treatment groups throughout the 14-day study period, but time was a significant ($P < 0.001$) overall effect. There was no significant effect of treatment on dyspnea score or coughing score; however, dyspnea and coughing were rarely observed.

There was no significant overall effect of treatment during the study period

Table 1—Least squares mean and SE clinical scores (range of possible scores, 0 [subjectively normal] to 3 [markedly abnormal]) and BW in 48 shelter-housed cats with clinical signs of URTD over the 14-day study period.

Variable	Treatment group				P value			
	Amoxicillin-clavulanic acid	Cefovecin	Doxycycline	SE	Repeated-measures ANOVA			Friedman χ^2 (treatment)
					Treatment	Time	Treatment \times time	
Oculonasal discharge score	1.19 ^a	1.52 ^a	0.59 ^b	0.15	< 0.001	< 0.001	0.14	< 0.001
Sneezing score	0.68 ^a	1.04 ^b	0.76 ^a	0.08	0.007	< 0.001	0.32	< 0.001
Dyspnea score	0.03 ^a	0.02 ^a	0.02 ^a	0.01	0.60	0.11	0.54	0.38
Coughing score	0.11 ^a	0.12 ^a	0.07 ^a	0.03	0.37	0.16	0.74	0.24
Demeanor score	0.31 ^a	0.44 ^a	0.37 ^a	0.06	0.28	< 0.001	0.005	< 0.001
Food intake score	0.46 ^a	0.60 ^a	0.67 ^a	0.10	0.23	< 0.001	0.021	< 0.001
BW (kg)								
Day 1	3.55 ^a	3.50 ^a	3.50 ^a	0.23	0.72	< 0.001	0.076	NA
Day 7	3.82 ^{*a}	3.50 ^a	3.55 ^a	0.23	NA	NA	NA	NA
Day 14	4.05 ^{*a}	3.68 ^a	3.82 ^{*a}	0.23	NA	NA	NA	NA

Cats were randomly assigned to 3 treatment groups ($n = 16/\text{group}$) on day 1: amoxicillin-clavulanic acid (12.5 mg/kg [5.68 mg/lb], PO, q 12 h, for 14 days), cefovecin (8.0 mg/kg [3.64 mg/lb], SC, once), or doxycycline (10.0 mg/kg [4.55 mg/lb], PO, q 24 h, for 14 days). Clinical evaluations were performed twice daily after day 1. Between days 3 and 9, 9 cats (3/treatment group) were removed from the study when the choice of antimicrobial was changed because of apparent treatment failure. Score data were globally ranked (rank transform procedure) before applying repeated-measures ANOVA. Body weight was reported for cats ≥ 1 year old.

*Value is significantly ($P < 0.05$) different from the day 1 value.

NA = Not applicable.

^{a,b}Within a row, values with different superscript letters are significantly ($P < 0.05$) different among treatment groups.

on demeanor score or food intake score (Table 1). However, there was a significant interaction effect of treatment group with demeanor score ($P = 0.005$) and food intake score ($P = 0.021$). The first significant ($P < 0.002$) decrease in demeanor score, compared with the day 1 value for the same group, was detected on day 2 for the amoxicillin-clavulanic acid group, day 5 for the cefovecin group, and day 7 for the doxycycline group (Figure 3). A significantly ($P < 0.002$) decreased food intake score, compared with the day 1 value for the same group, was first detected on day 2 for the amoxicillin-clavulanic acid group, day 10 for the cefovecin group, and day 11 for the doxycycline group (Figure 4).

Discussion

The study reported here identified improvement in the clinical health of cats enrolled in all 3 treatment groups over the 14-day study period, as determined by use of several semiquantitative clinical indicators. Illness severity scores are useful tools to decrease bias and confounding, provide quantitative and objective measures of patient illness, and demonstrate effective randomization in clinical trials, particularly when group sizes are small.²⁷ The random allocation of cats to treatment groups used in this study resulted in an equal distribution of cats among treatment groups in terms of age, rectal temperature at admission, sex, and clinical scores on day 1. This distribution also reduces the potential for bias in comparisons made among treatment groups.

Oculonasal discharge score is perhaps the most likely clinical variable to be affected by antimicrobial treatment because a maximum score (3/3) was allocated to cats with mucopurulent discharge (usually denoting infection with a bacterial component). The overall oculonasal discharge score was significantly lower in cats treated with doxycycline (10.0 mg/kg, PO, q 24 h) for 14 days than in those treated with amoxicillin-clavulanic acid (12.5 mg/kg, PO, q 12 h) for 14 days or with cefovecin (8.0 mg/kg, SC) once. This could be attributable to inferior clinical efficacy by the other 2 antimicrobials against *Mycoplasma* spp infections, compared with doxycycline, because samples collected from those cats in those groups (especially nasal swabs) yielded a high proportion of *Mycoplasma* isolates. Additionally, overall sneezing score was lower in the doxycycline and amoxicillin-clavulanic acid groups than in the cefovecin group. Doxycycline and amoxicillin-clavulanic acid have in vitro efficacy against *B bronchiseptica*¹³ and clinical efficacy against *C felis*.^{28,12} Susceptibility results from the study reported here also indicated that the *B bronchiseptica* isolates obtained were susceptible to doxycycline and amoxicillin-clavulanic acid but resistant to cefovecin. Although susceptibility testing for *Mycoplasma* spp is not available on a routine basis, isolates are generally susceptible to antimicrobials in the tetracycline group.¹⁴ Because *Mycoplasma* spp lack a cell wall,²⁹ they are resistant to antimicrobials that act by disrupting bacterial cell wall synthesis, such as β -lactams.³⁰ Another shelter-based study¹ found that the most important contributors to URTD in cats were FHV and *Mycoplasma* spp, although there is some controversy regarding the clinical relevance of *Mycoplasma* spp detection

because some studies have indicated the presence of *Mycoplasma felis* in healthy cats³¹ and others report its isolation only from the conjunctiva of diseased cats.³² However, both *Mycoplasma* spp and *C felis* have been reported as primary pathogens of the feline conjunctiva,^{33,34} and *B bronchiseptica* has been reported as a primary pathogen in the feline upper respiratory tract.^{35,36} In the study reported here, *Mycoplasma* spp and *B bronchiseptica* were the most commonly recovered isolates, and this may have contributed to the significantly lower oculonasal discharge and sneezing scores in cats treated with doxycycline, compared with other treatment groups. Alternatively, the solubilizing agent used for the doxycycline liquid, which included B-vitamin supplementation, could potentially have been responsible for some apparent treatment effect, but this seems unlikely. However, given that there was no significant difference between treatment groups in the number of days from intake to being deemed suitable for adoption on the basis of physical examination findings after the study had ended (approx 26 days from day 1 to adoption overall), it could be argued that in the long term, treatment made no difference to the final outcome. To test this hypothesis, an untreated control group would be needed and cats from each treatment group would have to be kept in an identical manner until considered healthy enough for adoption, but this would be difficult to justify on ethical grounds.

Cats in the present study were affected by 2 stressful events that could be expected to reduce their appetites and affect feeding behavior: the development of clinical signs of URTD and relocation to a new shelter environment. The LSM demeanor and food intake scores gradually improved over the course of the study from generally quiet and lethargic with a mildly reduced appetite (compared with expected consumption) to behaviors and food intake expected in relaxed, healthy cats that are acclimated to their environment. Body weight increased in cats (≥ 1 year old) in the amoxicillin-clavulanic acid and doxycycline groups during the study period, but those in the amoxicillin-clavulanic acid group had significantly higher BW by day 7 of the study. Considering that the cats were received from a large municipal shelter, it is possible that many of them were strays, and access to shelter and regular meals could explain some of the increase in these variables, as could growth in juvenile (< 1 year old) cats. There was also a significant interaction detected for treatment group with demeanor score and food intake score, with an apparently shorter time to a significant reduction in these scores in cats treated with amoxicillin-clavulanic acid. Increasing food intake indicates recovery from illness, and gustatory behavior is believed to be an important contributor to overall quality of life in owned and shelter-housed pets.³⁷ Reducing the duration of clinical signs of URTD could also increase the number of cats that can be moved through the shelter system to adoptive homes over time, thereby increasing the potential life-saving capacity of the shelter.

After a single SC injection of cefovecin, plasma and tissue transudate concentrations of the unbound drug remain greater than the MIC₉₀ for target pathogens for ≥ 14 days.¹⁸ Twice-daily examinations of the oral cavity were performed for each cat in the study reported here,

thereby reducing one of the possible benefits of cefovecin treatment because administration of the single-dose injectable drug would likely cause less handling stress, compared with oral administration of drugs. Additionally, no cats in the cefovecin group were determined to be infected with *B bronchiseptica*, and all of the *Bordetella* isolates in the present study were resistant to cefovecin in vitro. If some of the cefovecin-treated cats had been infected by *Bordetella* spp, it is possible that the clinical scores for the group could have been adversely affected. It should be noted that the mix of pathogens in this group of cats also may not have been representative of pathogens responsible for URTD in other shelters, and different degrees of efficacy might be found in other contexts or in a larger study.

In veterinary practice, the relative cost of suitable drugs is sometimes a factor in the choice of an antimicrobial, and this especially applies in a shelter situation, where funds are often limited. On the basis of purchase costs and treatment protocols used in the present study (calculated for cats weighing approx 4 kg [8.8 lb]), doxycycline was the least expensive treatment, with cefovecin being approximately 3 times as expensive (provided that a full 25-dose vial was used once reconstituted) and amoxicillin-clavulanic acid being approximately 6 times as expensive. This is a crude and incomplete estimate of treatment costs because the cost of labor required for drug administration and the potential loss of expired drug should also be included in an economic analysis. Cefovecin is relatively expensive to purchase, and it is currently marketed in a vial that, when the product is reconstituted, contains enough drug to administer to approximately 25 (4-kg) cats and has a shelf life of 28 days if stored away from light at 4°C. However, labor costs associated with drug administration are much less with a single injectable dose of cefovecin than with drugs such as doxycycline or amoxicillin-clavulanic acid, which require oral administration once and twice daily, respectively. Apart from the reduction in staff time, the ability to treat cats less frequently can potentially reduce stress for the cat and reduce the opportunity for fomite transmission by staff in the shelter.

Economic calculations are also affected by individual circumstances, such as the frequency and volume of antimicrobial administration in a veterinary practice or shelter, availability of unpaid volunteer labor in a shelter, and importance of issues potentially associated with orally administered drugs (eg, stress caused to ill cats and possible poor compliance because of difficulties with administration). Future studies examining treatment efficacy in cats housed in shelters would benefit from a detailed economic analysis taking into consideration other primary outcomes of interest to the shelter, such as time from intake to adoption.

A major limitation of the study reported here was the lack of an untreated control group for comparison with the 3 antimicrobial groups, but ethical concerns prevented this. A control group would have enabled us to discern whether antimicrobial treatment was beneficial in adult cats with clinical signs of URTD, given that the major pathogens involved are usually viral¹ and the immune response may be sufficient to eliminate some bacterial infections in otherwise healthy adult cats. In

other studies^{1,4} of shelter cats with URTD, primary viral infections with FHV and FCV were common, leading us to hypothesize that in the population of shelter cats in the present study, bacterial pathogens for which antimicrobial treatments could be effective might not have been of primary clinical importance. This supposition remains untested. The decision to implement antimicrobial treatment for treatment of URTD in cats in an animal shelter should be made judiciously by the attending veterinarian and should be part of a population management program that includes biosecurity, sanitation, vaccination, and housing protocols. Another limitation of the study was the lack of masking of personnel responsible for recording clinical scores during the study. This could have been a source of bias in the study if the observers wanted, or expected, one treatment to be superior to the others. We could speculate that shelter workers would be most likely to prefer cefovecin to be superior because cefovecin is the most convenient drug to use in a busy shelter situation. Conversely, observers could potentially have been biased against cefovecin treatment because they had positive opinions about amoxicillin-clavulanic acid or doxycycline treatment through prior experience or because they did not see cats in the cefovecin group receiving treatment.

There were temporal differences in the enrollment schedule for the 3 groups, but care was taken to preserve the random allocation of cats to treatment groups, which resulted in an equal distribution of all major study variables at enrollment. Although the prevalence of URTD pathogens can vary over time in a shelter, to the authors' knowledge, there is no evidence from the published literature that the pathogens of interest in URTD in cats have seasonal prevalence patterns. Additionally, because cats were enrolled in the amoxicillin-clavulanic acid group and the cefovecin group at the same times during the study, temporal differences in the enrollment schedule would only have had limited effects on any comparisons between the groups.

In the shelter-housed feline population studied, amoxicillin-clavulanic acid or doxycycline appeared to be effective treatments for URTD with a bacterial component. Infections with *B bronchiseptica* and *Mycoplasma* spp are somewhat common in shelter-housed cats with clinical signs of URTD¹; doxycycline, amoxicillin-clavulanic acid, or both are effective treatments against *B bronchiseptica*, and doxycycline is effective against *Mycoplasma* spp.^{13,14,16} In the authors' opinions, these drugs are suitable first-choice treatments for URTD in shelter-housed cats.

- a. Fort Dodge Fel-O-Guard Plus 3, Fort Dodge, Iowa.
- b. SNAP FIV/FeLV Combo test, IDEXX Laboratories Inc, Westbrook, Me.
- c. BBL culture swab, Collection and Transport system, BD Diagnostics, Sparks, Md.
- d. Research Randomizer, version 3.0, Urbaniak GC and Plous S. Available at: www.randomizer.org. Accessed Jun 5, 2012.
- e. Clavamox Drops, Pfizer Animal Health, New York, NY.
- f. Convenia, Pfizer Animal Health, New York, NY.
- g. Vibramycin, 50-mg doxycycline hyclate capsules, Pfizer Animal Health, New York, NY.
- h. VAL syrup, Fort Dodge Animal Health, Fort Dodge, Iowa.
- i. Hill's Science Diet Adult Optimal Care Original Cat Food (canned and dry food), Hill's Pet Nutrition Inc, Topeka, Kan.
- j. Vitek Biomerieux Inc, Durham, NC.

- k. Sensititre, Trek Diagnostics System, Cleveland, Ohio.
- l. Diffco *Mycoplasma* Broth, BD Diagnostic Systems, Franklin Lakes, NJ.
- m. KPL Inc, Gaithersburg, Md.
- n. *Mycoplasma* Culture Repository, International Research Programme on Comparative Mycoplasmology, West Lafayette, Ind.
- o. PROC FREQ, SAS, version 9.2, SAS Institute Inc, Cary NC.
- p. PROC GLM, SAS, version 9.2, SAS Institute Inc, Cary, NC.
- q. PROC MIXED, SAS, version 9.2, SAS Institute Inc, Cary, NC.
- r. PROC FREQ, SAS, version 9.2, SAS Institute Inc, Cary, NC.

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Appendix

Clinical scoring system used to subjectively assess signs of URTD in 48 shelter-housed cats that were randomly assigned to 3 treatment groups (n = 16/group): amoxicillin-clavulanic acid (12.5 mg/kg [5.68 mg/lb], PO, q 12 h, for 14 days), cefovecin (8.0 mg/kg [3.64 mg/lb], SC, once), or doxycycline (10.0 mg/kg [4.55 mg/lb], PO, q 24 h, for 14 days).

Variable	Score			
	0	1	2	3
Oculonasal discharge score	No ocular or nasal discharge	Small amount of serous ocular or nasal discharge	Large amount of serous ocular or nasal discharge	Mucopurulent discharge
Sneezing score (over a 30-min period)	No sneezing	Sneezes 1–2 times	Sneezes 3–4 times	Sneezes ≥ 5 times
Dyspnea score	Normal respiratory effort	Mild dyspnea; mildly increased respiratory effort with no abdominal component	Moderate dyspnea; some abdominal component	Severe dyspnea; marked abdominal component
Coughing score (over a 30-min period)	No coughing	Coughs 1–2 times	Coughs 3–4 times	Coughs ≥ 5 times
Demeanor score	Bright, alert, reactive	Quiet, lethargic	Has signs of depression but responds to human contact	Has severe signs of depression; demeanor doesn't change in response to human contact
Food intake score*	Eating normally	Mildly reduced appetite	Moderately reduced appetite	Anorexic

*Food intake was compared with expected consumption for cats of the same age and size, on the basis of the staff member's experience.