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Evaluation of antimicrobial prescriptions in dogs with suspected bacterial urinary tract disease

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Abstract

Background: Antimicrobials are commonly used to treat urinary tract disease in dogs. Understanding antimicrobial use is a critical component of antimicrobial stewardship efforts.

Hypothesis/Objectives: To evaluate antimicrobial prescriptions for dogs diagnosed with acute cystitis, recurrent cystitis, and pyelonephritis.

Animals: Dogs prescribed antimicrobials for urinary tract disease at veterinary practices in the United States and Canada.

Materials and Methods: A retrospective review of antimicrobial prescriptions was performed.

Results: The main clinical concerns were sporadic bacterial cystitis (n = 6582), recurrent cystitis (n = 428), and pyelonephritis (n = 326). Amoxicillin/clavulanic acid (2702, 41%), cefpodoxime (1024, 16%), and amoxicillin (874, 13%) were most commonly prescribed for sporadic bacterial cystitis. The median prescribed duration was 12 days (range, 3-60 days; interquartile range [IQR], 4 days). Shorter durations were used in 2018 (median, 10 days; IQR, 4 days) compared to both 2016 and 2017 (both median, 14 days; IQR, 4 days; $P \leq .0002$).

Amoxicillin/clavulanic acid (146, 33%), marbofloxacin (95, 21%), and cefpodoxime (65, 14%) were most commonly used for recurrent cystitis; median duration of 14 days (range, 3-77 days; IQR, 10.5 days). Amoxicillin/clavulanic acid (86, 26%), marbofloxacin (56, 17%), and enrofloxacin (36, 11%) were most commonly prescribed for pyelonephritis; however, 93 (29%) dogs received drug combinations. The median duration of treatment was 14 days (range, 3-77 days; IQR, 11 days).

Conclusions and Clinical Importance: Decreases in duration and increased use of recommended first-line antimicrobials were encouraging. Common drug choices and durations should still be targets for antimicrobial stewardship programs that aim to optimize antimicrobial use, concurrently maximizing patient benefits while minimizing antimicrobial use and use of higher tier antimicrobials.

Abbreviations: CIA, critically important antimicrobial; HIA, highly important antimicrobial; HP-CIA, highest priority critically important antimicrobial; ISCAID, International Society for Companion Animal Infectious Diseases; WHO, World Health Organization.

KEYWORDS
antimicrobial resistance, antimicrobial stewardship, infectious diseases, urinary tract infection

1 | INTRODUCTION

Infectious urinary tract disease is commonly diagnosed in dogs and accounts for abundant antimicrobial use.[1] Both lower (eg, cystitis) and upper (pyelonephritis) urinary tract disease can be encountered and empirical treatment decisions are typically made when initiating antimicrobial treatment. The dearth of high level evidence comparing different treatment regimens complicates antimicrobial selection in companion animals. Properly designed randomized clinical trials, which provide the highest level of evidence, are scarce. Increasingly, there is interest in national or international clinical practice guidelines, akin to what is available in human medicine.[2] While currently driven by expert opinion, veterinary guidelines, based on data from companion animals, data from other species and general principles of microbiology, pharmacology, infectious diseases, and internal medicine can provide guidance to practitioners and improve clinical care in the absence of high level data. In 2011, International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for the diagnosis and treatment of bacterial urinary tract disease were released,[3] with an updated version released in 2019.[4] The impact of guidelines has not been properly evaluated and is difficult to study.

Antimicrobial stewardship is an area that is getting increasing attention in veterinary and human medicine, as the magnitude and scope of antimicrobial resistance become clear. Antimicrobial resistance is also a One Health problem that requires study of all components of the One Health triad—humans, animals, and the environment. Antimicrobial use in any area can contribute to resistance, with resistant bacteria and resistance genes moving among animals, humans, and the environment. Antimicrobial stewardship aims to optimize antimicrobial therapy, maximizing clinical outcomes while minimizing adverse effects on the patient (eg, gastrointestinal complications) or population (eg, selection pressure for antimicrobial resistance).[5-7] Concerns about the public health impacts of antimicrobial use in animals add more pressure to optimize use of antimicrobials in all species. A core component of antimicrobial stewardship is improved understanding of when and how antimicrobials are used. Understanding antimicrobial use patterns is critical for determining potential areas for improvement and intervention, and to facilitate an evidence-based approach to stewardship activities. Establishment of baseline rates (benchmarking) is necessary for comparisons and to evaluate the impact of interventions. The objective of this multicenter study was to evaluate initial antimicrobial therapy in dogs diagnosed with upper or lower urinary tract infections.

2 | MATERIALS AND METHODS

A query was performed from the medical records system of a veterinary practice corporation with clinics in the United States and Canada. The query involved canine cases from 2 January 2016 to 3 December 2018 that were either diagnosed with a urinary tract infection, cystitis, pyelonephritis, as well as more colloquial diagnoses such as kidney and bladder infection. Cases where the clinician had a suspicion of the prior diagnoses listed were included in the query. Only the cases where there was an identified antibiotic administered to the patient were included for further analysis. Signalment, age, breed, reproductive status, weight, practice location, visit date, diagnosis, and antimicrobial drug regimens were retrieved. Initial prescriptions were recorded. Subsequent prescriptions were only included if they were a continuation of the initial therapy. Dogs that were presented for new complaints at least 60 days from the previous visit were considered independent cases, an empirical decision based on a goal of avoiding classifying dogs that did not adequately respond to their initial episode as a repeated incident, while capturing true new disease events.

The open entry diagnostic field in the medical record was evaluated and cases were classified into sporadic bacterial cystitis, recurrent/chronic cystitis (referred to herein as recurrent cystitis), pyelonephritis, urolithiasis, emphysematous cystitis, and other. The number of visits of an individual patient was not used to assign cases to the "recurrent/chronic" group since the goal was to evaluate veterinarians' decision-making based on their assessment (eg, if a patient had 3 visits but the veterinarian still reported this as sporadic cystitis, the case was classified as sporadic bacterial cystitis because that was how the veterinarian approached the case). Numerous descriptions were used in the open entry field, necessitating a subjective determination in some cases. This was performed while blinded to other data fields (eg, drug, duration). Entries that indicated "suspect" or "possible" were considered because they were accompanied by an antimicrobial prescription. When entries indicated the potential presence of a comorbidity that might impact antimicrobial decision-making (eg, vaginitis, prostatitis), the data for that individual were removed. Antimicrobial duration was determined based on specific prescription recommendations (eg, administer for 14 days), or, when that was not available, calculated based on the recommended dose (eg, "give 2 tablets twice daily") and amount of drug that was dispensed. The duration field was left blank if there was inadequate information to accurately determine duration, but records were retained for analysis of drug selection. For evaluation of duration, each dose of cefovecin was considered to be a 14-day-treatment duration.[8] Because of the small proportion of prescriptions from specialty clinics, analysis based on clinic type was not performed.

Outcomes of interest were antimicrobial prescribed and duration of treatment. Further analysis was performed categorizing antimicrobials as per World Health Organization criteria,[9] assigning antimicrobials into the highest priority critically important antimicrobial (HP-CIA), critically important antimicrobial (CIA), and highly

important antimicrobial (HIA) groups. Prescription practices were compared to 2011[3] and 2019[4] ISCAID guidelines, to determine if they were or were not consistent with these guidelines. Geographic comparisons were based on US postal regions (total of 9 regions in the United States) and the entire country of Canada, because of small sample sizes for some US states and the smaller Canadian sample size.

Continuous data were evaluated for normality using Shapiro-Wilk (for sample sizes ≤2000) or KSL (Kolmogorov-Smirnov test with Lilliefors correction) tests (for sample sizes >2000). Non-normally distributed data were reported as median and interquartile range (IQR). Associations of categorical data were assessed using chi-square and Fisher's exact tests, while continuous data were analyzed using Wilcoxon, Steel, or Steel-Dwass tests. For all analyses, $P < .05$ was considered significant. When 5 or more comparisons were performed, Benjamini-Hochberg-adjusted *P*-values (*Q* values) were determined. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Data were analyzed using JMP14 (SAS Institute, Cary, North Carolina). Network analysis was performed in R[10] using igraph (http://igraph.org).

3 | RESULTS

A total of 7803 antimicrobial prescriptions from 7387 dogs were evaluated. There were 7127 dogs from 673 clinics from the United States and 260 dogs from 50 clinics in Canada. The number of animals per clinic ranged from 1 to 123 in the United States (median, 7; IQR, 12) and 1 to 31 (median, 3; IQR, 5.5) in Canada. Small numbers from some clinics reflected either small caseloads or later introduction of the standardized medical record system. Most (623, 94%) were primary care clinics, 20 (3.0%) provided both primary and specialty care while 21 (3.1%) were specialty hospitals. Overall, 6971 (89%) of prescriptions were from primary care clinics, 517 (6.6%) were from clinics offering both primary and specialty care, and 315 (4.0%) were from specialty clinics. The main clinical concerns were sporadic bacterial cystitis (n = 6582/7387, 89%), recurrent cystitis (n = 428, 5.7%), and pyelonephritis (n = 326, 4.4%). Other conditions were not analyzed further because of the smaller sample sizes (n = 51 total). Treatment duration was available for 7635/7803 (98%) prescriptions from 7245/7387 (98%) dogs.

4 | SPORADIC BACTERIAL CYSTITIS

The study population was comprised of 6582 dogs. The majority (4892, 74%) were spayed females, with 941 (14%) neutered males, 378 (5.7%) intact females, and 223 (3.4%) intact males. Sex was not provided for 135 (2.1%) dogs. The median age was 7.5 years (range, 0.1-20.8 years; IQR, 7.85 years). There was a total of 6866 antimicrobial prescriptions; 6324 dogs (96%) were prescribed 1 antimicrobial, while 251 (3.8%) received 2 and 7 (0.1%) received 3 antimicrobials.

Seventeen different antimicrobials were reported. The most commonly prescribed antimicrobials (covering 6252 of the 6582 dogs; 95%) are presented in Table 1 and Figure 1. A variety of antimicrobial combinations was used (Table 2). Network analysis of antimicrobial combinations for drugs used in a combination at least 5 times is presented in Figure 2.

A total of 2699 (39%) of prescriptions were for HP-CIAs, 3760 (55%) for CIAs, and 407 (5.9%) for HIAs. Forty percent (2622/6582) of dogs received 1 or more HP-CIAs.

The 2011 ISCAID guidelines recommended amoxicillin or trimethoprim/sulfonamide (TMS) as first-line treatments, with amoxicillin/clavulanic acid as a drug that is an "acceptable option but not

TABLE 1 The most commonly prescribed antimicrobials for dogs with sporadic cystitis (n = 6582), recurrent cystitis (n = 428), and pyelonephritis (n = 326)

Sporadic bacterial cystitis		Recurrent cystitis		Pyelonephritis	
Amoxicillin/clavulanic acid (CIA)	2702 (41%)	Amoxicillin/clavulanic acid (CIA)	131 (31%)	Amoxicillin/clavulanic acid (CIA)	86 (26%)
Cefpodoxime (HP-CIA)	1024 (16%)	Marbofloxacin (HP-CIA)	83 (19%)	Marbofloxacin (HP-CIA)	56 (17%)
Amoxicillin (CIA)	874 (13%)	Cefpodoxime (HP-CIA	58 (14%)	Enrofloxacin (HP-CIA)	36 (11%)
Marbofloxacin(HP-CIA)	584 (8.9%)	Amoxicillin (CIA)	44 (10%)	Amoxicillin/clavulanic acid + enrofloxacin (HP-CIA)	25 (7.7%)
Enrofloxacin (HP-CIA)	350 (5.3%)	Enrofloxacin (HP-CIA)	32(7.5%)	Amoxicillin/clavulanic acid + marbofloxacin (HP-CIA)	22 (6.7%)
Cefovecin (HP-CIA)	327 (5.0%)	Cefovecin (HP-CIA)	19 (4.5%)	Cefovecin (HP-CIA)	21 (6.4%)
Cephalexin (HIA)	219 (3.3%)	Cephalexin (HIA)	14 (3.3%)	Amoxicillin (CIA)	15 (4.6%)
Ciprofloxacin (HP-CIA)	66 (1.0%)	Trimethoprim-sulfamethoxazole (HIA)	7 (1.6%)	Amoxicillin/clavulanic acid + doxycycline (CIA)	6 (1.8%)
Trimethoprim-sulfamethoxazole (HIA)	58 (0.9%	Amoxicillin/clavulanic acid + marbofloxacin (HP-CIA)	7 (1.6%)	Cefovecin + marbofloxacin (HP-CIA)	6 (1.8%)
Amoxicillin/clavulanic acid + marbofloxacin (HP-CIA)	48 (0.7%)	Ciprofloxacin (HP-CIA)	5 (1.1%)	Orbifloxacin (HP-CIA)	5 (1.5%)

Abbreviations: CIA, critically important antimicrobial; HIA, highly important antimicrobial (World Health Organization, 2019); HP-CIA, highest priority critically important antimicrobial.

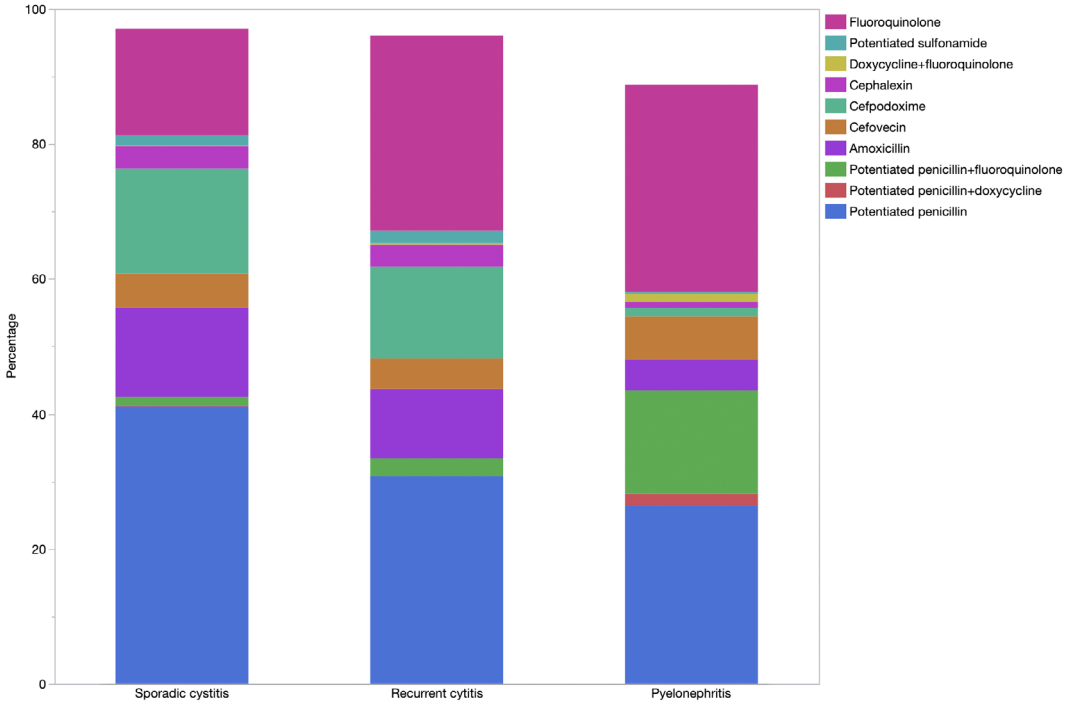

FIGURE 1 Stacked bar graph of the median percentage of prescriptions of the main 6 drug classes or combinations for treatment of sporadic bacterial cystitis (n = 6582), recurrent cystitis (n = 428), and pyelonephritis (n = 326)

TABLE 2 The most commonly used antimicrobial combinations in dogs treated for sporadic bacterial cystitis (n = 6582), recurrent cystitis (n = 428), and pyelonephritis (n = 326)

Sporadic bacterial cystitis	Recurrent cystitis	Pyelonephritis
Amoxicillin/clavulanic acid + marbofloxacin (48, 0.7%)	Amoxicillin/clavulanic acid + marbofloxacin (7, 1.6%)	Amoxicillin/clavulanic acid + enrofloxacin (25, (7.7%)
Amoxicillin/clavulanic acid + cefpodoxime (33, 0.5%)	Amoxicillin/clavulanic acid + enrofloxacin (3, 0.7%)	Amoxicillin/clavulanic acid + marbofloxacin (22, 6.7%))
Amoxicillin/clavulanic acid + enrofloxacin (26, 0.4%)	Amoxicillin/clavulanic acid + cefpodoxime (2, 0.5%)	Amoxicillin/clavulanic acid + doxycycline (6, 1.8%)
Amoxicillin/clavulanic acid + cefovecin (24, 0.4%)	Amoxicillin + cefpodoxime (2, 0.5%)	Cefovecin + marbofloxacin (6, 1.8%)
Cefovecin + cefpodoxime (12, 0.2%)		Cefovecin + enrofloxacin (4, 1.2%)

recommended initially," while the 2019 ISCAID guidelines[4] added amoxicillin-clavulanic acid as a first-line option. If just amoxicillin and TMS are considered, 14% (932) dogs over the entire study period received a recommended first-line drug. There was no significant difference between 2016 (52% [736/1410]) and 2017 (53% [1348/2536], OR 1.04, 95% CI 0.91-1.18, $P = .57$), but there was a significant increase by 2018 (59% [1550/2636], 2017 compared to 2018 OR 1.26, 95% CI 1.13-1.40, $P < .0001$), 2016 compared to 2018 (OR 1.31, 95% CI 1.15-1.49, $P < .0001$). Changes in the prescription of the main drug classes are presented in Table 3.

Overall, the median duration of drug prescription was 12 days, with a range of 3 to 60 days, IQR of 4 days, and a mode of 14 days (Figure 3). Only 151/6500 (2.3%) dogs received ≤5 days, the recommended duration in the 2019 ISCAID guidelines. However, 2011 ISCAID guidelines (which would have been applicable at the time these cases were seen) recommended 7 to 10 days duration and 1295 (20%) dogs received ≤7 days, with 3074 (47%) treated ≤10 days. Eighty-nine percent (5808/6500) received ≤14 days. The median duration was 14 days (IQR, 4 days) in 2016 and 2017 and 10 days (IQR, 4) in 2018. There was a significant difference in duration between 2016 and 2018 ($P = .0002$) and 2017 and 2018 ($P < .0001$), but not 2016 and 2017 ($P = .95$).

5 | RECURRENT CYSTITIS

Four hundred fifty-five antimicrobials were prescribed to 428 dogs. The population consisted of 335 (79%) spayed females, 55 (13%) neutered males, 24 (5.9%) intact females, and 10 (2.4%) intact males. Reproductive status was not reported for 4 dogs. The median age was 8.6 years (range, 0.17-21 years; IQR, 6.7 years).

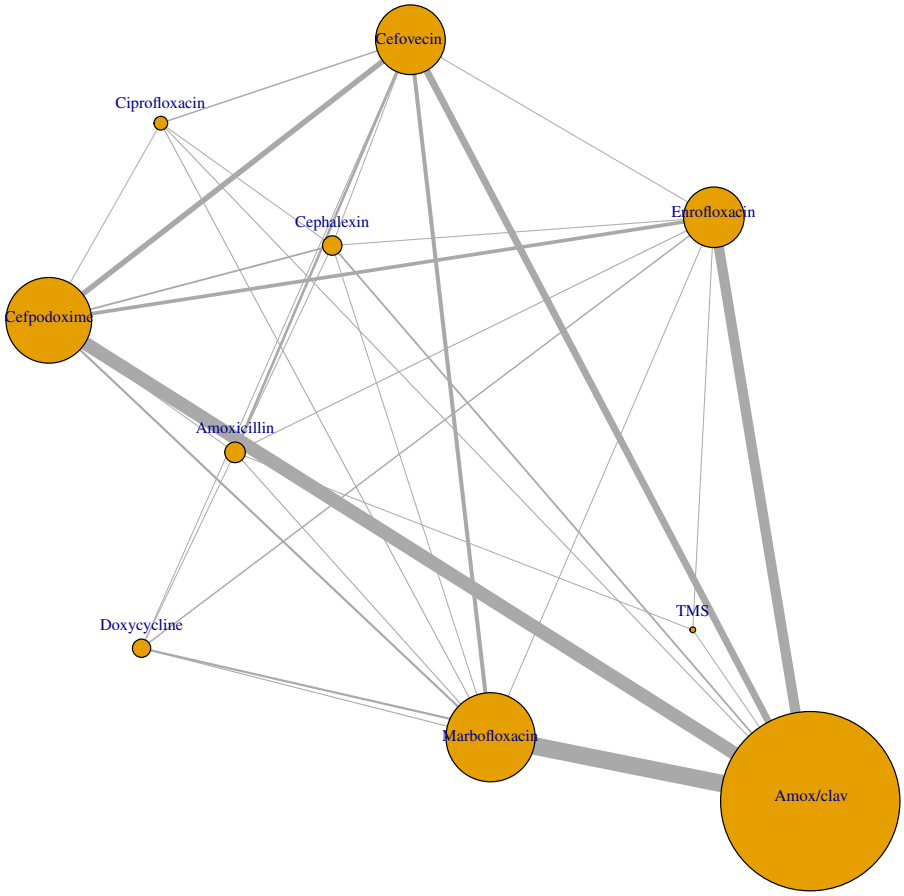

FIGURE 2 Network diagram of combination antimicrobial use in dogs that received more than 1 antimicrobial for the treatment of sporadic bacterial cystitis (n = 258). Node size reflects the relative number of prescriptions. Line width depicts the degree of association

TABLE 3 Odds ratios (OR)[a], 95% confidence intervals (95% CI), and Q values for changes in prescription of antimicrobial classes to dogs diagnosed with sporadic bacterial cystitis between 2016 and 2018

Antimicrobial	2016-2017: OR (95% CI), Q value	2017-2018: OR (95% CI), Q value	2016-2018: OR (95% CI), Q value
Amoxicillin 2016: 144/1410 (10%) 2017: 333/2536 (13%) 2018: 410/2636 (16%)	**1.35 (1.11-1.65), Q = 0.015**	1.18 (1.01-1.37), Q = 0.0555	**1.59 (1.31-1.94), Q = 0.0005**
Potentiated penicillin 2016: 614/1410 (44%) 2017: 1043/2536 (41%) 2018: 1178/2636 (45%)	0.91 (0.80-1.03), Q = 0.350	**1.15 (1.03-1.27), Q = 0.0267**	1.04 (0.92-1.18), Q = 0.1.00
3rd-generation cephalosporins			
Cefovecin 2016: 94/1410 (6.7%) 2017: 158/2536 (6.2%) 2018: 137/2636 (5.2%)	0.93 (0.71-1.21), Q = 0.59	0.83 (0.65-1.04), Q = 0.11	0.77 (0.58-1.01), Q = 0.055
Cefpodoxime 2016: 242/1410 (17%) 2017: 454/2536 (18%) 2018: 404/2636 (15%)	1.05 (0.89-1.25), Q = 0.56	**0.83 (0.72-0.86), Q = 0.013**	0.87 (0.73-1.04), Q = 0.13
Fluoroquinolones 2016: 248/1410 (18%) 2017: 412/2536 (16%) 2018: 391/2636 (15%)	0.90 (0.77-1.06), Q = 0.352	0.97 (0.84-1.11), Q = 0.652	0.87 (0.74-1.03), Q = 0.500
Potentiated sulfonamides 2016: 24/1410 (1.7%) 2017: 41/2536 (1.6%) 2018: 35/2636 (1.3%)	0.97 (0.60-1.58), Q = 0.960	0.76 (0.49-1.18), Q = 0.275	0.73 (0.45-1.23), Q = 01.00

Bold was used to highlight statistically significant results (Q < 0.05).
[a]Reference group is the earlier year of the comparison.

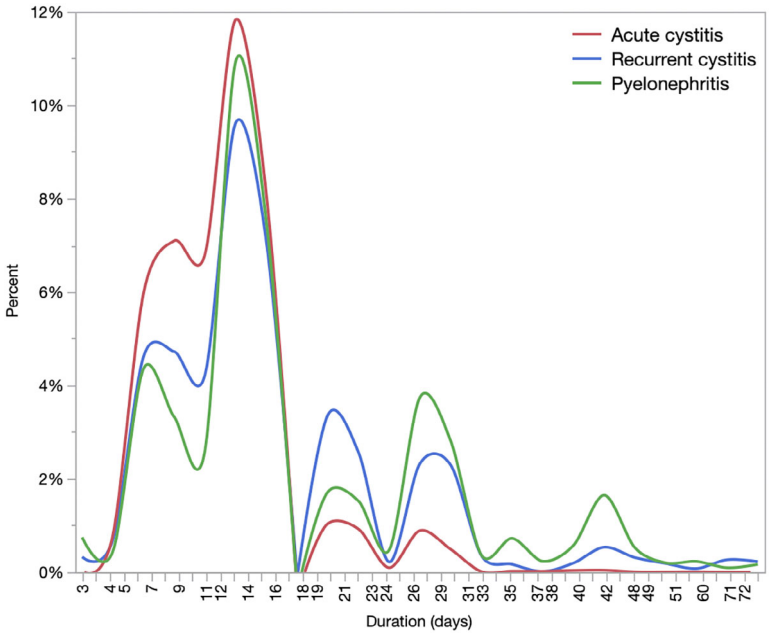

FIGURE 3 Smoothed line graph comparing the duration of antimicrobial prescription for dogs with sporadic bacterial cystitis (n = 6582), recurrent cystitis (n = 428), and pyelonephritis (n = 326)

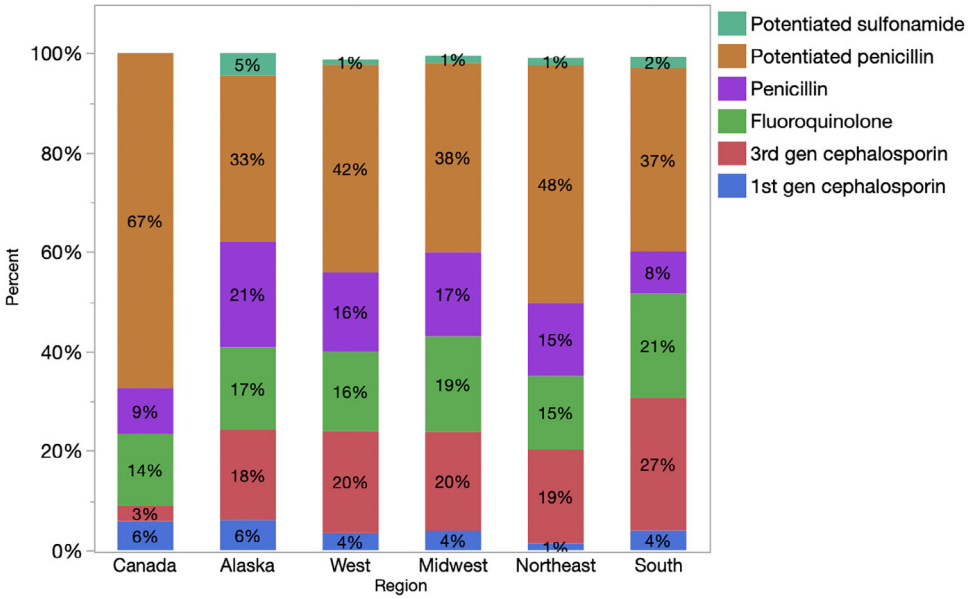

FIGURE 4 Regional comparison of prescription of drug classes in dogs diagnosed with sporadic bacterial cystitis (n = 6582)

In total, 16 different antimicrobials were prescribed, with amoxicillin-clavulanic being the most commonly described drug (Tables 1 and 2; Figure 1). Twenty-five (5.8%) dogs received combination therapy. The median and mode durations were 14 days, with a range of 3 to 77 days and IQR of 10.5 days (Figure 3).

One or more HP-CIAs were administered to 224 (52%) dogs. In total, 51% (230/454) prescriptions were for HP-CIAs, 42% (191) for CIAs, and 7.3% (33) for HIAs.

6 | PYELONEPHRITIS

Four hundred twenty-five antimicrobials were prescribed to 326 dogs. These consisted of 188 spayed females (58%), 93 neutered males (29%), 21 intact males (6.4%), and 18 intact females (5.5%). Sex was not reported for 5 (1.5%). Amoxicillin/clavulanic acid was the most commonly prescribed treatment (86 [26%]; Table 1; Figure 1); however, combination therapy was common, with 91 (28%) dogs receiving 2 antimicrobials and 2 (0.6%) receiving 3 (Table 2). Fluoroquinolones are the recommended first-line treatment[4] and 181 (56%) dogs received a fluoroquinolone, alone or as part of a combination. Fourteen (4.3%) dogs received doxycycline or minocycline, alone or as part of a combination. Most (207, 63%) dogs received 1 or more HP-CIAs. Overall, HP-CIAs accounted for 228 (54%) of prescriptions, followed by CIAs (171, 40%) and HIAs (26, 6.1%). The median and mode duration of treatment were 14 days (IQR, 11 days), with a range of 3 to 77 days.

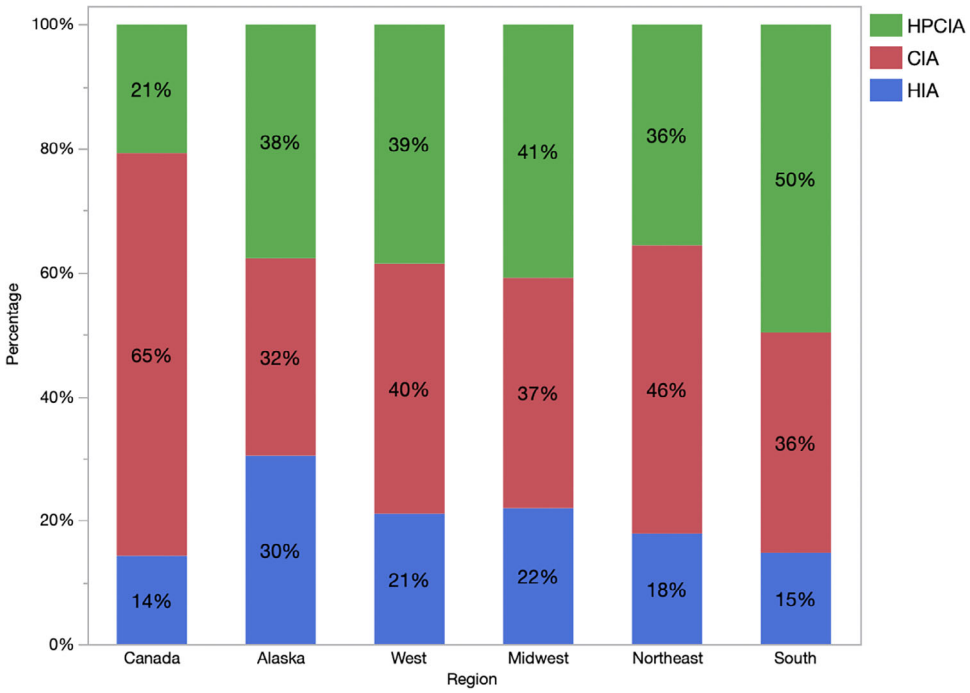

FIGURE 5 Regional comparison of prescription of World Health Organization antimicrobial categories in dogs diagnosed with sporadic bacterial cystitis (n = 6582). CIA, critically important antimicrobial; HIA, highly important antimicrobial; HP-CIA, highest priority critically important antimicrobial

TABLE 4 Comparison of the use of highest priority critically important antimicrobials (World Health Organization, 2019) in dogs with sporadic bacterial cystitis (n = 6582) between Canada and US census regions

Region; n/N (%)	Referent; n/N (%)	Odds ratio	95% confidence interval	*P* value
Alaska; 22/66 (33%)	Canada; 36/221 (16%)	2.3	1.3-4.1	.005
Midwest; 435/1174 (37%)	Canada	2.6	1.9-3.7	<.0001
Northeast; 361/1092 (33%)	Canada	2.1	1.5-3.0	<.0001
South; 976/2132 (46%)	Canada	3.8	2.7-5.2	<.0001
West; 653/1897 (34%)	Canada	2.4	1.7-3.3	<.0001

7 | NATIONAL AND REGIONAL COMPARISONS

There were differences in antimicrobial drug selection between Canada and the United States for recurrent cystitis ($P = .006$), sporadic bacterial cystitis ($P < .001$) (Figure 4), but not pyelonephritis ($P = .76$). These corresponded with higher HP-CIA drug use for sporadic bacterial cystitis in the United States (2447/6361, 38%) vs Canada (36/221, 16%) (OR 2.4, 95% CI 1.7-3.4, $P < .001$; Figure 5; Table 4).

8 | DISCUSSION

Bacterial urinary tract disease is commonly diagnosed in dogs and is a frequent indication for antimicrobial use; therefore, it is an important target for antimicrobial stewardship activities. These data provide broad information about the use of antimicrobials in dogs diagnosed with bacterial cystitis and pyelonephritis and highlight potential areas for future interventions.

Empirical drug selection is almost always used when treating suspected bacterial upper or lower urinary tract disease, either because urine cultures are not performed or because treatment is initiated while awaiting culture results. The predominant causes of bacterial cystitis in dogs are members of the Enterobacteriaceae family, particularly *Escherichia coli*, with staphylococci tending to be the next most prevalent group.[11,12] Therefore, empirical antimicrobial choices should reach therapeutic levels in urine and be active against those bacterial groups. From pharmacological and microbiological standpoints, beta-lactams and fluoroquinolones are excellent options. However, while 3rd-generation cephalosporins and fluoroquinolones are excellent drugs from a likely treatment efficacy standpoint for cystitis, they are classified as HP-CIA and evidence of benefits over drugs in lower categories (eg, amoxicillin) are lacking.

There are some clinical situations where these drugs would be reasonable choices (eg, inability to administer oral medications, need for once daily dosing), but they are not recommended for first time use,[3,4] and the high frequency of use noted here suggests that they are overused. The 39% prevalence of HP-CIA use in sporadic bacterial cystitis is presumably well beyond what is necessary or ideal and is a prime target for intervention.

Overall, drug choices identified in this study for sporadic bacterial cystitis were similar to studies in Canada and Denmark, where amoxicillin-clavulanic acid was most common.[1,13] In this study, slightly over 50% of prescriptions for sporadic bacterial cystitis were consistent with ISCAID treatment guidelines,[3,4] indicating ample room for improvement, but similar to results from an Australian study that surveyed veterinarians' responses to an acute lower urinary tract infection scenario.[14] First-line recommendations do not necessarily apply to all cases (eg, resistant bacterial infections, dogs that are unable to be medicated PO, dogs that are intolerant of first-line antimicrobials); however, it is reasonable to assume those exceptions would constitute a small percentage of the population, leaving ample room for improvement. Interestingly, there was an increase in prescription of first-line drugs over time, increasing from 52% to 59% over a fairly short (2016-2018) period of time. Reasons for this are unclear. Possible explanations could include increasing awareness of antimicrobial stewardship, continuing education regarding treatment of urinary tract infections, and increasing awareness of guidelines. The inter-regional differences were also interesting. Potential explanations such as differences in education (if the distribution of where people obtained their veterinary education differed between regions), recommendations of regional experts and differential access or exposure to continuing education should be explored. It is important to investigate differences based on time, geography, and other factors to help understand what drives decision-making and to facilitate future interventions.

Duration of treatment of sporadic bacterial cystitis was relatively long, particularly when the most recent guideline recommendations (3-5 days)[4] are considered. Ten to 14 days of treatment was most commonly used here, similar to a Danish study that reported a median duration of 10 days.[13] While high level data are lacking, there is evidence that shorter durations (eg, 3-5 days) are as effective as longer durations,[15,16] something that is consistent with the current approach in human medicine.[2] The use of shorter durations reduces cost, risk of adverse effects, antimicrobial resistance selection pressure, and probably optimizes compliance (as compliance presumably wanes with longer courses). There was a decrease in duration of treatment over the study period. As for drug selection, reasons for the shift in drug selection are unknown but as with the increase in use of first-line drugs, this is an encouraging finding, despite the relatively small numerical change.

Differences in durations for different drugs for both sporadic bacterial and recurrent cystitis, with significantly shorter duration of use of amoxicillin-clavulanic acid compared to many drugs, were interesting. It is possible that people who choose a first-line drug such as amoxicillin-clavulanic acid are more likely aware of shorter duration recommendations, but this is purely speculative.

Recurrent cystitis has been defined as dogs having 3 or more episodes of cystitis in a year, or 2 or more episodes in the preceding 6 months.[4] In this study, categorization was based on clinicians' data entry so a standard definition could not be applied. "Complicated" cystitis has also been used,[3] but there is not a clear definition of what "complicated" means and there is a need to differentiate complicated infections (which might require longer or different treatments) from simple infections in complicated dogs (with comorbidities but which might respond to treatment used for sporadic cases). This range of cases within the "recurrent cystitis" group may explain the broader range of durations that were used compared to sporadic bacterial cystitis, with common use of 14 days of treatment but relatively frequent use of longer (eg, 21 or 28 days) courses.

Pyelonephritis is a potentially life-threatening infection of renal parenchyma that requires a different approach than cystitis. For pyelonephritis, *E coli* predominates and tissue (not urine) antimicrobial drug levels are important. Fluoroquinolones are recommended as first-line treatments in dogs,[4] yet only 56% of dogs received a fluoroquinolone. Some dogs diagnosed with pyelonephritis received relatively short (≤7 days) courses of treatment. This could reflect reconsideration of the diagnosis after further testing or assessment of response to treatment. The 14-day median duration noted here is shorter than the 4 to 6 week recommendation in the 2011 ISCAID guidelines, but closer to the 2019 guidelines that recommended 10 to 14 days. Relatively common prescription of amoxicillin-clavulanic acid for pyelonephritis raises concerns. While excellent for bacterial cystitis because of the high drug levels in urine, pyelonephritis is an infection of tissue, not urine. Clinical and Laboratory Standards Institute (CLSI) guidelines[17] state that apart from lower urinary tract infection, Enterobacterales should be reported as resistant to amoxicillin-clavulanic acid (as well as ampicillin and amoxicillin) because inadequate drug levels are achieved in tissue. Similarly, while cefovecin monotherapy for pyelonephritis was infrequent, there are no CLSI breakpoints for Enterobacterales in tissue, reflecting the questionable ability of cefovecin to reach effective concentrations for Enterobacterales in tissue.

Combinations of antimicrobials were prescribed in 3.8% (sporadic bacterial cystitis) to 28% (pyelonephritis) cases. Combinations of cefovecin and PO administered drugs were interesting. While uncommon, there is little justification from an antimicrobial spectrum standpoint to combine this cephalosporin with another 3rd-generation cephalosporin (n = 16), amoxicillin-clavulanic acid (n = 26), or a fluoroquinolone (n = 31). A major indication for the use of cefovecin is for patients that cannot be medicated PO, something that would not be consistent with combined use with an oral antimicrobial. Combination therapy can be useful when broad spectrum treatment is needed, but it is uncommonly required in treatment of urinary tract disease, and the combinations noted here would not have extended the antimicrobial spectrum much. Some combinations highlighted in Figure 2 are potentially synergistic combinations (eg, beta-lactam plus a fluoroquinolone) that are more understandable from pharmacologic basis but would rarely be needed or useful in urinary tract disease. Unnecessary combination increased cost, client effort, risk of adverse effects, risk of drug interactions, and broader antimicrobial exposure of the commensal microbiota. Reducing combinations, especially those that have highly redundant antimicrobial spectra, is warranted. The use of doxycycline as part of a combination for treatment of pyelonephritis likely reflects concern about leptospirosis, in cases where doxycycline was used in combination with an antimicrobial that

is more typically used for pyelonephritis (eg, a fluoroquinolone). Other combinations are harder to explain and probably indicate at least some degree of unnecessary and redundant antimicrobial use.

The frequent use of HP-CIAs also raises concern. There is no single approach or classification of antimicrobials and various regional (eg, European Medicines Agency [EMA]) and national classifications also exist. However, a constant aspect of different guidelines is the classification of fluoroquinolones and 3rd-generation cephalosporins as high tier agents. Thus, whether they are referred to as "HP-CIA" (WHO), "Restrict" (EMA, https://www.ema.europa.eu/en/news/categorisation-antibiotics-used-animals-promotes-responsible-use-protect-public-animal-health) "Critically important" (US Food and Drug Association, https://www.fda.gov/files/animal%20&%20veterinary/published/CVM-GFI--152-Evaluating-the-Safety-of-Antimicrobial-New-Animal-Drugs-with-Regard-to-Their-Microbiological-Effects-on-Bacteria-of-Human-Health-Concern.pdf), or "Very high importance" (Canadian Veterinary Drug Directorate, https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/antimicrobial-resistance/categorization-antimicrobial-drugs-based-importance-human-medicine.html), there is consistency in placement of these drug classes in high tiers where use should be scrutinized. While largely developed based on concerns regarding food animals, concerns should also apply to use in companion animals.

Drug data are presented at the individual drug, drug class, and WHO categorization level. In addition to the issues discussed above related to drug categorization, there can be differences within drug classes. Most notably for these data, while both cefovecin and cefpodoxime are 3rd-generation cephalosporins, they do not have identical antibacterial spectra. Cefovecin has lesser activity against Enterobacterales such as *E coli* and is not recommended for use against *E coli* in tissue because levels above the MIC90 for *E coli* are not achieved in vivo (https://www.zoetisus.com/products/dogs/convenia/assets/pdf/Convenia_PI.pdf). However, this would be of limited impact when evaluating the use of these drugs for cystitis because of high urinary excretion, and both drugs are licensed for use in cystitis in some countries. As discussed above, cefovecin is not an appropriate option for empirical treatment of pyelonephritis because of its poor activity against *E coli* in tissue.

This study was based on retrospective review of electronic records, something that is associated with various inherent limitations. Detailed medical record data were not available, so factors that might have influenced decisions could not necessarily be identified. Disease categorizations were also based on initial assessment and were based on free text entry, requiring subjective interpretation in some situations. Many cases were reported as "possible" or "suspected" infections but were included because an antimicrobial was prescribed and the goal was to assess empirical antimicrobial use, not scrutinize diagnoses. Changes made after prescription would not always be reflected in the database; however, these data still indicate the prescribers' recommendations at the time of patient examination. Culture and susceptibility data were not available alongside prescription data and it is unknown how often urine culture was performed in this population. Regardless, the data collected indicated the initial therapy, something that would not be impacted by whether or not culture was performed. Culture results could have impacted duration of use if treatment was extended based on positive cultures. This could not be further investigated. Outcome data were not available, so treatment efficacy could not be assessed. It is likely that some dogs with noninfectious lower urinary tract disease were included. However, since veterinarians diagnosed these as having bacterial cystitis and prescribed an antimicrobial, misdiagnosis would not presumably impact the results, as the study assessed prescribers' actions when they thought that a bacterial disease was likely present, irrespective of whether that was truly the case. Changes in diagnoses made after the results of diagnostic testing were not captured. Longer durations that occurred based on poor initial clinical response were also not necessarily identified if a drug change was not made. Detailed medical record review would be ideal for more refined categorization and interpretation, but was not possible based on the design and size of the study. While there were likely some errors in categorization, it is assumed that they represented a small percentage of cases. Nonparametric analyses limit the impact of outliers so while, for example, a long duration for sporadic bacterial cystitis could be true or miscategorization, the impact of rare data points like those would be minimal. It is likely that some dogs classified as having sporadic bacterial cystitis were truly acute recurrences of chronic or recurrent disease, given the long durations of treatment that were present in a few cases.

These data provide important and broad baseline information regarding common practices for the treatment of bacterial cystitis and pyelonephritis. Bacterial urinary tract disease is a prime target for antimicrobial stewardship programs that aim to optimize antimicrobial use, concurrently maximizing patient benefits while minimizing overall antimicrobial use and use of HP-CIAs. The potential for numerous targeted interventions are apparent here, including measures to increase the use of first-line antimicrobials, reduce the use of redundant combinations, and decrease treatment duration.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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