Antimicrobial resistance is a topic of global concern, with overuse, inappropriate use, and agricultural use of antimicrobials combined with a decrease in the development of new antimicrobials having created an antimicrobial resistance crisis. The finite supply of known antimicrobial agents means that resistance on any level, individual or otherwise, can have important consequences to human and animal public health. Efforts to combat antimicrobial resistance in the human and animal sectors include a CDC initiative to prevent infections, monitor resistance, promote the rational use of antimicrobials, and develop new antimicrobials and testing standards to combat antimicrobial resistance. While food or production animal medicine has been targeted as an area in which decreased antimicrobial use can have an impact, efforts are also being made in veterinary companion animal medicine to promote awareness of this issue at the organizational level, provide guidelines for antimicrobial use, and empower companion animal veterinarians to become better stewards of antimicrobial medications.

Urinary tract infections (UTIs), or bacterial cystitis, occur commonly in dogs, with approximately 14% of dogs developing a UTI in their lifetime. Given the frequent occurrence of this problem, it offers a broad platform from which to examine the antimicrobial prescribing practices of small animal veterinarians in primary care medicine.
private practice in the United States. Guidelines published by the International Society for Companion Animal Infectious Disease (ISCAID) on antimicrobial use for companion animal UTIs, published in June 2011 and updated in May 2019, have provided evolving guidance over time, moving from general recommendations about antimicrobial choice and dosage, including preferential selection of amoxicillin to treat uncomplicated, or sporadic, UTIs,9,10 to recommendations for a decreased duration of antimicrobial treatment and avoidance of antimicrobials when they are not justified.10 Continued examination of prescribing patterns and the results of these actions are indicated as part of surveillance efforts for antimicrobial use.13–15

The present study aimed to describe patterns of antimicrobial prescriptions for sporadic UTIs in dogs in the United States from 2010 through 2019, including times before and after publication of the ISCAID guidelines, to determine any changes in the proportion of UTIs treated with various antimicrobials during that time period and ascertain if the proportion of dogs with urinary tract disease for which an antimicrobial was not prescribed changed over time. Special attention was paid to the recommended first-line antimicrobials for treating UTI (amoxicillin, amoxicillin–clavulanic acid, and trimethoprim-sulfonamides) and the antimicrobials recommended to be reserved for infections for which use of first-line antimicrobials is not appropriate16 that, like amoxicillin and amoxicillin–clavulanic acid, have been designated as critically important antimicrobials by the World Health Organization.16

Materials and Methods

We used the electronic medical records of a private veterinary corporation consisting of > 1,000 primary care clinic locations across the United States. Records for a 10-year period (2010–2019) were searched to identify all dogs with new clinical signs compatible with UTI that had been active patients in the electronic medical records for ≥ 6 months prior to developing signs of UTI, unless they were < 6 months of age. For this population of dogs, a visit for potential sporadic UTI was defined as a single visit between January 1, 2010, and December 31, 2019, during which there was a diagnostic code indicative of UTI or cystitis or signs of a UTI (eg, stranguria, dysuria, or hematuria) were recorded. Visits were excluded if information for the preceding 6 months was not included in the electronic medical record to ensure these dogs had not had a previous UTI within that period of time. Dogs were also excluded if the visit for a potential sporadic UTI occurred < 6 months after a previous visit for a potential UTI, or if they had been prescribed any antimicrobial in the preceding 2 months. Dogs listed as having an age ≤ 0 were considered implausible and were also excluded from analyses. It was possible that a given dog might have qualified for inclusion more than once over the course of the study period.

Statistical analysis

Descriptive statistical analyses were performed with commercial software (SAS, version 9.4; SAS Institute). All potential sporadic UTI visits that qualified for inclusion were counted in the total number, including those that did not result in an antimicrobial prescription. For potential sporadic UTI visits, we checked all antimicrobial prescriptions made on the same day as the visit to limit analyses to only those prescriptions associated with the qualifying event. Antimicrobial prescriptions were quantified by counting the total number of prescriptions for each qualifying event. We allowed for > 1 antimicrobial prescription for a single visit.

To enhance visual clarity, prescriptions were graphed by month and year over the 10-year period as the proportion of the number of patients for which no antimicrobial or a given antimicrobial was prescribed versus the total number of qualifying UTI visits. These graphs included intercepts for the months of publication of the ISCAID guidelines in 2011 and 2019 to highlight any changes occurring around the time of guideline publication. A log-linear regression model with the number of visits without an antimicrobial prescription as the dependent variable and time as the independent variable, offset by the log of the total number of UTI visits, was used to indicate trends over time and calculate 95% CIs for potential UTI visits during which no antimicrobials were prescribed.

Log-linear regression was used to conduct interrupted time series analyses for the aminopenicillins (amoxicillin, amoxicillin–clavulanic acid, and ampicillin), the antimicrobials recommended in the ISCAID guidelines as first-line treatments for uncomplicated UTIs, with the 2011 guidelines as the interruption to assess the impact of these guidelines on prescribing trends for these antimicrobials before and after guideline publication. A model was created for each of the aminopenicillins that included the number of antimicrobial prescriptions as the dependent variable, while the number of visits, the date of guideline publication (represented as a dummy variable), and a term indicating the interaction between the number of visits and the date of guideline publication were the independent variables, offset by the log of the total number of UTI visits.

Results

A total of 461,244 qualifying visits for potential sporadic UTI were examined, with 389,949 (85%) of these visits resulting in at least 1 antimicrobial prescription; the remaining 71,295 (15%) visits resulted in no antimicrobial prescription. The modeled trend for the proportion of potential sporadic UTI visits that resulted in no antimicrobial prescription showed a small increase over the 10-year period (0.5% increase on an annual basis; P < 0.01; Figure 1), with larger changes in the observed annual proportions over this time (14% in 2010 to 19.7% in 2019; Supplementary Table S1).
The highest proportions of prescriptions were seen with the aminopenicillins, a recommended first-line class of antimicrobials, with the majority of those prescriptions being amoxicillin–clavulanic acid, ranging from 36% to 48% (Figure 2) and the proportion of amoxicillin prescriptions increasing from 2.5% in 2010 to 10% in 2019. The proportion of ampicillin prescriptions decreased sharply from 2010 to the time of the 2011 guidelines publication, with monthly proportions starting at 22% and decreasing to 7%. Following this time, the proportion continued to decrease to almost 0 by the end of 2019. The other first-line antimicrobial group, the trimethoprim-sulfonamides (used broadly to include trimethoprim-sulfadiazine, trimethoprim-sulfamethoxazole, and ormetoprim-sulfadimethoxine), showed lower use, with the proportion of these prescriptions never rising above 1.5% (Figure 3).

The cephalosporins and fluoroquinolones, listed as antimicrobials to be used only in specific cases in the 2019 guidelines, comprised the second and third largest prescription groups, respectively (Figures 4 and 5). The first-generation cephalosporins (ie, cephalaxin, cefadroxil, and cefazolin) had very little use, with the proportion of prescriptions never higher than 2% and a slight decrease in use over time, whereas the third-generation cephalosporins (ie, cefovecin and cefpodoxime) had more variability and generally higher proportions of prescriptions overall, ranging from 11% to 21% at the high end and 4 to 8% at the low end.

For the fluoroquinolones, there was a sharp decrease in the use of enrofloxacin (ranging from just over 10% to just under 2% of prescriptions) at the
same time there was a sharp increase in the use of marbofloxacin (ranging from just under 1% to just over 6% of prescriptions) from 2010 to publication of the 2011 guidelines. Proportions of ciprofloxacin and orbifloxacin prescriptions were just under 1%.

Interrupted time series analysis for the amoxicillin–clavulanic acid and the log-linear regression line obtained by means of interrupted time series analysis; publication of the first ISCAID guideline in June 2011 was used as the interruption for time series analysis.
Amoxicillin
0.989 (0.868–1.127)
0.87

Amoxicillin–clavulanic acid
0.993 (0.947–1.042)
0.78

Ampicillin
0.476 (0.426–0.532)
< 0.01

-5 to 4%, \( P = 0.78 \) to a significant 0.5% increase in slope per year following guidelines publication (95% CI, 0.2% to 0.8%; \( P < 0.01 \)). Use of ampicillin increased much more dramatically. The slope for ampicillin was decreasing rapidly toward 0 prior to publication of the 2011 guidelines, with a 52% decrease in slope per year (95% CI, -57% to -47%; \( P < 0.01 \)), but the slope increased sharply at the time of guidelines publication, slowing to a 32% decrease per year after guidelines publication (95% CI, -34% to -30%; \( P < 0.01 \)).

**Discussion**

In general, results of the present study suggest that veterinary primary care practitioners in this private corporation changed their antimicrobial prescribing practices for sporadic UTIs over the 10-year period from 2010 to 2019. Although the recommendation to decrease the use of antimicrobials overall was more specific in the 2019 guidelines than in the 2011 guidelines, small but persistent changes were seen in the proportion of sporadic UTI visits that resulted in no antimicrobial prescription. Changes were also seen in those visits resulting in an antimicrobial prescription, with increasing proportions of prescriptions for amoxicillin and amoxicillin–clavulanic acid, in accordance with the 2011 ISCAID guidelines. Amoxicillin–clavulanic acid and amoxicillin alone were predominant prior to publication of the 2011 guidelines, and there was a trend toward a further increase in their use following the 2011 guidelines publication. Although the 2011 ISCAID guidelines were less positive about the use of amoxicillin–clavulanic acid, compared with other choices, it was still listed as an acceptable first-line antimicrobial. That recommendation was revised in the 2019 guidelines to read, “if amoxicillin without clavulanic acid is not readily available, use of amoxicillin/clavulanic acid is reasonable.”

Approached from the lens of the current 2019 guidelines, this trend in increasing use is a positive finding. Additional support for the use of amoxicillin–clavulanic acid can be seen in a study\(^9\) that found that although the addition of clavulanic acid reduces the abundance of bacteria that are considered part of the beneficial microbiota, amoxicillin and amoxicillin–clavulanic acid have similar effects on antimicrobial resistance in fecal samples from dogs.

Our finding was consistent with studies in the United States showing that amoxicillin–clavulanic acid is frequently prescribed for both unspecified reasons\(^8\) and UTIs.\(^4\) Following publication of the ISCAID guidelines, there were small but persistent changes that continued in the same direction, with the rate of annual change increased more for amoxicillin than for amoxicillin–clavulanic acid as determined with the interrupted time series analysis. Given the lack of evidence for an advantage of amoxicillin–clavulanic acid, compared with amoxicillin alone, for treatment of uncomplicated UTIs and the desire to choose the most specific and efficacious antimicrobial possible,\(^8\) the differential rates of increase for these antimicrobials are encouraging evidence of increasing veterinary antimicrobial stewardship. Changes in ampicillin use seemed to be heavily influenced by the 2011 guidelines; however, the reason for the initial decrease in use is not known.

Unlike amoxicillin and amoxicillin–clavulanic acid, it is difficult to draw conclusions about use of the other recommended first-line antimicrobial class, the trimethoprim-sulfonamide combinations, because of their much smaller proportions of use. These drugs started as a seldom-chosen antimicrobial and showed a further decline in use. Although they have been shown to be effective with a short duration of treatment,\(^10\) which may limit adverse effects,\(^10\) the presence of these adverse effects, which can be very serious and include idiosyncratic and immune-mediated reactions,\(^11,12\) may be a reason these antimicrobials are less frequently chosen.

In contrast, a steady, small proportion of prescriptions were for fluoroquinolones, with use of marbofloxacin seemingly replacing that of enrofloxacin in 2010. This use represented a much smaller proportion than for the third-generation cephalosporins, were
used more frequently than the fluoroquinolones, but the first-generation cephalosporins were not used as frequently. These findings are contrary to the 2019 ISCAID guidelines but may reflect the convenience of dosing and administration for these medications. For example, one of these drugs (cefepodoxime) is an oral medication that is administered once daily, compared with twice daily administration for cephalaxin, amoxicillin-clavulanic acid, and amoxicillin, and the other (cefotaxime) is given as a single injection that lasts for multiple days. Typically, cefotaxime is used in cats, which can be notoriously difficult to medicate, but this may also be the case for some dogs that are difficult to medicate orally and for which owner compliance is a challenge. Additionally, other influences on antimicrobial selection may come into play, such as price, personal preference of the prescriber, and owner request.

One of the limitations of our analysis was assigning a causative role in changing prescribing patterns to publication of the ISCAID guidelines. The data seem to show changes in prescribing patterns at the time of guidelines publication, but it is possible that some of these changes may also have been due to other forces, such as formulary changes or availability of medications, rather than awareness of recommended guidelines. Drug selection for the private practices from which our data were obtained is guided by a common drug formulary. The formulary requires that medications available to the hospitals undergo a rigorous evaluation to assess the safety, efficacy, and validity of their label claims, in addition to evaluation of the supply chain and manufacturing processes. Owing to the complexity of the pharmaceutical landscape, availability of some medications may change over time, and therefore, the available medication portfolio may also change over time (J. A. Morrison, DVM, Banfield Pet Hospital, email, March 1, 2021). Although individual practitioners are able to prescribe a medication that is not included in the formulary, these medications are not routinely supplied in the individual hospitals and must be prescribed through an outside pharmacy. Additionally, it is also possible that knowledge of antimicrobial stewardship from other sources had an effect. However, as the interrupted time series analysis showed for the aminopenicillins (ie, increases in amoxicillin and amoxicillin-clavulanic acid use with a drastic slowing of the decrease in ampicillin use), changes that occurred at the time of guidelines publication continued over time. Notably, there is evidence that guidelines can change and improve clinical practice.

Even with thorough attention to detail, it is likely that not every antimicrobial prescription made was captured in the present study. Data were analyzed only for the date that the visit took place and do not account for antimicrobial medications prescribed in the few days after the visit or prescriptions obtained from outside pharmacies. Given the way the data were stored and presented, it was difficult to ensure that these cases would be correctly identified without some level of manual record analysis, which was beyond the scope of this study.

Ideally, an interrupted time series analysis would consist of equal numbers of time points before and after the interruption to more accurately estimate the change in trend. Even with this limitation, given the large number of data points and the relatively narrow CIs, the calculated interrupted time series graphs should be reasonably accurate.

Possibly the largest limitation of our study is generalizability. While the study population represents thousands of patients and prescriptions across the United States, there was uniformity in the use of a single formulary, and results, therefore, may not accurately represent the full diversity of antimicrobials used or the response to guidelines publication in other private veterinary practices. Even with this limitation, information on widespread prescribing practices for canine UTIs in the United States is useful, especially in the face of the small number of previous studies in this country.

Areas for further investigation include larger studies of prescribing patterns for nonassociated private primary care practices, as well as investigations of prescribing practices as they relate to empirical evidence of infection (eg, urinalysis and urine culture results), patterns of local and national antimicrobial resistance, and duration of antimicrobial prescriptions in relation to the 2019 ISCAID guidelines indicating 3 to 5 days as the recommended duration of treatment.

In conclusion, results of the present study suggest that for dogs with potential sporadic UTIs examined between 2010 and 2019 at clinics owned by this private corporation, the proportion of visits resulting in no antimicrobial prescription increased, in accordance with ISCAID guidelines, and use of recommended first-line antimicrobials (amoxicillin and amoxicillin-clavulanic acid) increased when antimicrobials were prescribed. Although there is still room for improvement, especially with regard to use of the medically important third-generation cephalosporins and fluoroquinolones, the data suggest that overall veterinarians in these private practices are taking their role as stewards of antimicrobial use seriously and are changing their prescribing practices to be more in accordance with published guidelines. Our findings help to characterize the prescribing patterns in veterinary private practices in the United States over the past 10 years to provide a baseline, to offer information on areas where antimicrobial stewardship is in need of improvement, and to allow us to detect any future changes in trends.

Acknowledgments

Dr. Bloch is employed part-time as a primary care clinician at a Banfield practice in North Carolina. Dr. Papich has served on International Society for Companion Animal Infectious Disease and Clinical and Laboratory Standards Institute committees as an unpaid consultant. He has been a paid consultant for Zoetis, Elanco, Merck, Boehringer-Ingelheim, and Bayer (now Elanco). Dr. Stürmer receives investigator-initiated research funding and support as a principal investigator (R01 AG056479) from the National Institute on Aging and as a coinvestigator (R01 HL118255 and R01 MD011680).
from the National Institutes of Health. He also receives salary support as Director of Comparative Effectiveness Research for the North Carolina Translational and Clinical Sciences Institute, from a University of North Carolina Clinical and Translational Science Award (UL1TR002489), from the Center for Pharmacoeconomics (current members: GlaxoSmithKline, UCB BioSciences, Takeda, AbbVie, and Boehringer Ingelheim), from pharmaceutical companies (Novo Nordisk), and from a generous contribution from Dr. Nancy A. Dreyer to the University of North Carolina at Chapel Hill Department of Epidemiology. Dr. Stürmer does not accept personal compensation of any kind from any pharmaceutical company. He owns stock in Novartis, Roche, and Novo Nordisk.

The authors thank Dr. Chris Wiesen, Senior Statistical Research Consultant at the Odum Institute for Research in Social Science at the University of North Carolina at Chapel Hill, for his expertise in statistical modeling. The authors also thank Virginia Pate and Dr. Olivia S. K. Chan for their contributions to this study.

References


Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org