

[An update on the duration of antibacterial treatment, are vets up to date?](#)

PART 2: RESEARCH PAPER

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Preface

I would like to thank my supervisors Jeroen Dewulf and Suzanne Dewulf for their guidance in writing this thesis, in particular regarding the design of the study.

Secondly, thanks to the veterinarians who did help me to collect the data. It was not easy to find participants for this study, since veterinarians nowadays are very occupied and experience a high workload. This made me appreciate even more that the participants of this study made time in their busy schedule to help me.

A special thank you to Reimer Wolff, who supported me in various ways throughout this project. You helped me take my project to the next level and working with you was hilarious and educational at the same time.

Of course, without the constant support of my wonderful family, I would not have come where I am today. I would like to thank them from the bottom of my heart for this. As I always say; teamwork makes the dream work!

Summary

The emergence of antimicrobial resistance necessitates that veterinarians prescribe antibiotic courses responsibly. To achieve this, antimicrobial stewardship should provide guidelines for the prudent use of antimicrobials for bacterial infections, which are available online on the website of the federal knowledge center on Antimicrobial Consumption and Resistance in Animals (AMCRA). Equally important as the evidence-based guidelines, is the prescription behavior of the small animal veterinarians in the field. The objective of this study was to assess the up-to-dateness of first-line Flemish veterinarians, regarding their prescription behavior in sporadic bacterial cystitis in female dogs. This condition was selected because it is an important contributing factor to the overuse of antibiotics. In literature, the advised treatment duration is three to five days and the guideline of AMCRA was adapted accordingly in 2019.

A retrospective case study and survey were performed. Strikingly, only 4% of the patients with sporadic bacterial cystitis were treated in accordance with the guideline, with 96% receiving a longer course of antibiotics. According to the survey, 30% prescribed an antibiotic course with a treatment duration of three to five days. The discrepancy between the self-assessment of the veterinarians and the retrospective case study, in combination with the prolonged treatment duration, indicates that first line veterinarians in Flanders can and should improve their prescription behavior to a more prudent use of antibiotics.

Samenvatting

De opkomst van antimicrobiële resistentie benadrukt het belang dat dierenartsen op een verantwoorde manier antibiotica voorschrijven. Hiervoor zijn er voor verschillende bacteriële infecties richtlijnen online beschikbaar op de website van het federaal kenniscentrum voor antibioticumgebruik en resistentie bij dieren (AMCRA). Van even groot belang als de op wetenschap gebaseerde richtlijnen is het voorschrijfgedrag van gezelschapsdierenartsen in de praktijk. Het doel van deze studie was om te analyseren of Vlaamse dierenartsen op de hoogte zijn van de laatste ontwikkelingen en richtlijnen in het geval van een sporadische bacteriële cystitis bij de teef. Deze aandoening werd gekozen omdat dit een van de aandoeningen is die een grote bijdrage levert aan het overmatig gebruik van antibiotica. In de literatuur wordt een behandelduur van drie tot vijf dagen aangeraden en de richtlijnen van het AMCRA zijn in 2019 hiernaar aangepast.

Deze studie is gebaseerd op een retrospectieve casestudie en een enquête. Uit de casestudie bleek dat slechts 4% van de patiënten met een sporadische bacteriële cystitis werd behandeld met een antibioticumkuur die qua duur overeenkomt met de richtlijn, de overige 96% kreeg een langere kuur voorgeschreven. Uit de enquête blijkt dat 30% een sporadische bacteriële cystitis behandelt met een kuur van drie tot vijf dagen. Het verschil tussen de zelfevaluatie van de dierenartsen en wat er uit de retrospectieve casestudie komt, in combinatie met de grote hoeveelheid dierenartsen die een te lange kuur voorschrijft, suggereert dat het van groot belang is dat Vlaamse eerstelijns dierenartsen hun voorschrijfgedrag verbeteren.

Keywords

Antimicrobial resistance – Antimicrobial stewardship – Sporadic bacterial cystitis – Treatment duration

Introduction

Recently there has been a lot of research into the prudent use of antibiotics. With an increasing prevalence of multidrug-resistant infections (Swanson, 2022), it is important that veterinarians apply the latest insights and guidelines. Are veterinarians up to date?

Antimicrobial resistance

Antimicrobial resistance (AMR) is a serious global threat that must be addressed rather sooner than later – as recognized by most clinicians. Without further action, AMR will have major consequences to both human medicine (Murray et al., 2022) and veterinary medicine (Bengtsson and Greko, 2014). Bacterial AMR originates when bacteria change in such a way that the antibacterial pathways no longer interfere with the bacterial genome or its proteins and will no longer result in stunted growth (bacteriostatic) or cell death (bactericide) of the bacteria (Christaki et al., 2020). Prudent use of antibiotics is essential to delay the emerge of AMR (Tenover, 2006).

One Health

Given the complexity and ecological nature of this problem, the One Health approach is necessary (McEwen and Collignon, 2018). Companion animals should not be overlooked in the One Health approach regarding AMR, since multidrug resistant (MDR) bacteria have been isolated in dogs and cats. Therefore, they represent a reservoir of resistance genes. This creates a potential risk for humans, considering the narrow contact between owners and their companion animals (Allerton et al., 2021). The notion of the interconnection between humans and animals has given rise to “antimicrobial stewardship” under the One Health initiative (Dyar et al., 2017). This system wide approach consists of three key points: the optimization of therapy, the prevention of overuse, misuse and abuse, and the minimization of the development of AMR (Davies et al., 2013). The goal of antibiotic stewardship is tailored prescription of antibiotics with extra attention for the indication, dose, route, and duration (Majumder et al., 2020). In the field of veterinary medicine, there is still room for improvement and obstacles to overcome in the implementation of antimicrobial stewardship (Hardefeldt et al., 2018). Current barriers include numerous knowledge gaps regarding dose-effect relationships between antimicrobial use and resistance, antimicrobial consumption, resistance prevalence, drug-to-drug superiority, and optimal duration of treatment (Guardabassi and Prescott, 2015).

Target selection versus collateral selection

The use of antibiotics is also subject to public misconceptions: for example, that therapy non-compliance is an important driving force for selecting resistance genes. Most prescribers erroneously warned their patients to “complete the course, even when you feel better” (Amábile-Cuevas, 2022). In a systematic review about the public’s knowledge and beliefs about antibiotic resistance, McCullough et al. found that a lot of people thought that excessive antibiotic use (70%) and not completing the course (62%) were the main reason of antibiotic resistance (McCullough et al., 2016). In a similar systematic review about the knowledge of clinicians even a higher percentage (90%) thought that patient non-adherence is an important driver of resistance (McCullough et al., 2015). In addition to that, the reason behind this slogan has been communicated with the public: if you do not finish your course, you will only tackle the weakest bacteria and the stronger ones will remain. When your infection reoccurs, this will be a more resistant population of bacteria and your infection will be

harder to treat.¹ This concept, where the selection for resistance is among the bacteria being treated, is known as target selection. This might be the mechanism behind the development of AMR for some pathogens, such as *Mycobacterium tuberculosis* or *Neisseria gonorrhoeae* when monotherapy or an incorrect dosage is used to treat the infection. However, this is of limited value for other infections (Llewelyn et al., 2017). The importance of collateral selection is increasingly known, where resistance emerges mostly off target, not at the infection site but among colonizing flora (Spellberg, 2016). The commensal flora can transfer their resistance genes to other (potential pathogen) bacteria (Christaki et al., 2020) (Fig. 1).

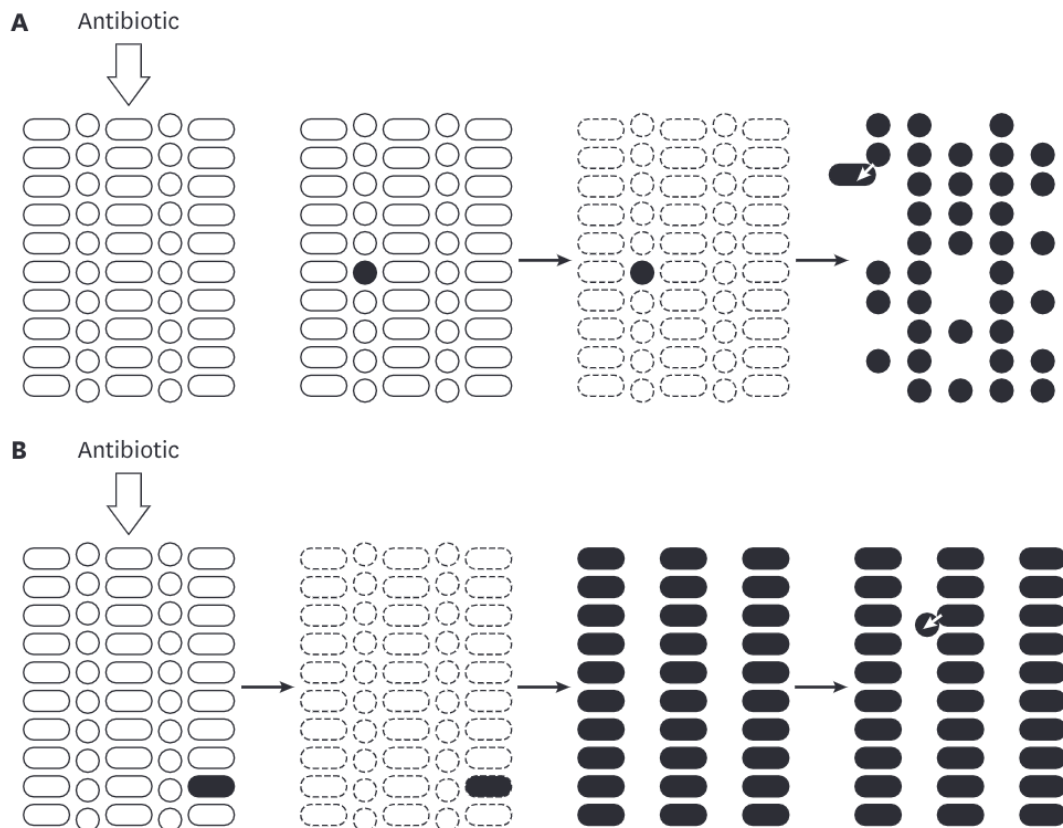


Figure 1. Target selection and collateral selection. Panel A shows target selection, as resistance was previously thought to develop. A susceptible population (open figures) of pathogenic bacteria (round figures) is treated with antibiotics. A bacterium becomes resistant (black figures), while the rest is killed by the antibiotic (broken outlines) and the resistant bacterium forms a resistant population at the site of infection. Panel B shows collateral selection, where resistance does not occur on the site of infection, but rather at the level of commensal bacteria (oval figures). This forms a reservoir of resistance genes, with the possibility that these will be passed on to other bacteria (Amábile-Cuevas, 2022).

Since the commensal bacteria (e.g., the intestinal flora) are affected by treating a patient with antibiotics (Crémieux et al., 2003), a longer antibiotic course duration will increase the selection pressure on the bacteria. Recognizing that selection pressure is the most important driving force behind the emergence of antibiotic resistance (McEwen and Collignon, 2018), finishing the course – even when the patient feels better – might jeopardize the battle against the rise of resistance

¹ ¹RIVM (Rijksinstituut voor Volksgezondheid en Milieu). Available online: <https://www.rivm.nl/antibioticaresistentie> (accessed on 28/03/2024).

(Spellberg, 2016). Therefore, according to the latest insights, antibiotics should not be continued once the infection is eradicated (Weese et al., 2015). A new mantra arises: “hit the infection hard and fast” (Swanson, 2022).

Treatment duration

However, resistance is not the only important factor when it comes to the duration of an antibiotic course. Clinical cure is the most important factor to conclude whether a therapy was successful (Havey et al., 2011). For most bacterial infections, the duration of the treatment is empirically established. A recent systematic review found short courses of antibiotics are as effective as longer courses for a variety of infections in human (Hanretty and Gallagher, 2018). In contrast to veterinary medicine, the antibiotic course duration has been shortened progressively in human medicine. In veterinary medicine, evidence on optimal treatment durations is limited (L.R. Jessen et al., 2019) and since comparisons with human treatment durations should be done with care, more studies are needed to provide evidence-based guidelines for the duration (Weese et al., 2015).

Sporadic bacterial cystitis

Sporadic bacterial cystitis is a common reason for use, and presumably also overuse and misuse of antimicrobials (Weese et al., 2019). In human medicine, since 1999, guidelines indicate that a three day antibiotic course is sufficient to treat uncomplicated cystitis in women (Warren et al., 1999). In female dogs, an empirical long-duration treatment (seven to fourteen days) has been the standard for years (Clare et al., 2014). However, three to five days of antibiotic treatment is sufficient to treat sporadic bacterial cystitis after performing a bacterial culture and susceptibility test (Mortier et al., 2021). This is in accordance with the trend to shorten antibiotic courses (Allerton et al., 2021), as well as the guidelines of the federal knowledge center on Antimicrobial Consumption and Resistance in Animals (AMCRA), which provides a formulary available online².

Aim of the study

Equally important as the presence of evidence-based guidelines, is its implementation by the veterinarians in the field. Therefore, the prescribing behavior of first line veterinarians in Flanders regarding antibiotics for sporadic bacterial cystitis in female dogs was investigated, as well as their knowledge about the latest guidelines using a survey. Additionally, retrospective cases of uncomplicated cystitis were included, and the treatment was compared to the answers from the survey. The aim of this study is to investigate whether the duration of the prescribed courses differ from the guidelines of AMCRA.

² Formularium AMCRA. Available online: <https://formularium.amcra.be/> (accessed on 01/03/2024)

Materials and methods

The quest for participants

First, a request via email was sent to 50 veterinary medicine students at the Ghent University currently following an internship, to include cases during their time at the veterinary clinic, as well as to ask the supervising veterinarians to complete the survey. Secondly, an email was sent to various veterinarians in Flanders, asking them to take part in the study. This was followed by a visit to different clinics. Then, 101 randomly selected veterinarians were called, requesting them to participate in the study. After agreement by telephone, an email containing the required information and an anonymous Qualtrics link was sent, followed by two reminders. For the survey, a Facebook message with a short introduction and the anonymous Qualtrics link was posted twice in three different private groups for veterinarians, reaching a total of 1200 practitioners.

Study design

Inclusion criteria were uncomplicated bacterial cystitis in female dogs of all ages, that were treated between January 2023 and March 2024 in Flanders. Complicated cystitis was an exclusion criterion. The information required was breed, age, spayed or not, history of cystitis, the symptoms, the presence of other medical conditions and used diagnostic tests. Additionally, the prescribed antibiotics and the duration of the treatment was specified. A signed confidentiality agreement was obtained per individual participating veterinarian, providing retrospective cases.

A survey was conducted among Flemish veterinarians that probed for the length of their prescribed courses for uncomplicated bacterial cystitis. Furthermore, it contained questions about which source of information was used for prescribing antibiotics, whether the guidelines of AMCRA were known and/or used, and whether the prescription behavior regarding uncomplicated bacterial cystitis in female dogs was changed in the past years. Next to that, one question was about in what circumstances the veterinarian would decide to prescribe a shorter course. A full version of this questionnaire is attached in appendix 1. Personal data – i.e. name of the veterinary clinic – was treated in a strictly anonymous way.

Statistical analysis

The data was analyzed using a Fisher's exact test. Statistical significance was set as $P < 0.05$. Graphpad Prism was used for the statistical analysis. To see whether there was a difference in prescription behavior depending on year of graduation, the group was divided into the veterinarians who graduated before 2019 and the veterinarians who graduated in 2019 or later. This graduation year was chosen because in this year, AMCRA last updated their guidelines.

Results

Response rate

From the clinics where students followed their internship, only two clinics could participate because a large proportion of the responders did not meet the geographical requirements. Those did not send any cases, but one veterinarian completed the survey. After emailing, only 4% of the randomly selected veterinarians in Flanders reacted. The response rate was increased to 14% after calling or visiting the veterinarians and sending multiple reminders. Three cases were excluded because they did not meet the inclusion criteria. A total of 26 cases from 14 different clinics were included. The survey was completed by 54 veterinarians.

Duration of the antibiotic course

Of all veterinarians, 69% used AMCRA as one of their resources for antibiotic stewardship, and 61% claimed to follow the guidelines. Around a quarter (26%) did not prescribe an antibiotic course to patients with sporadic bacterial cystitis. Of the veterinarians who prescribed antibiotics, 30% did so for three to five days. The remaining 70% prescribed a course of >5 days (Fig. 2).

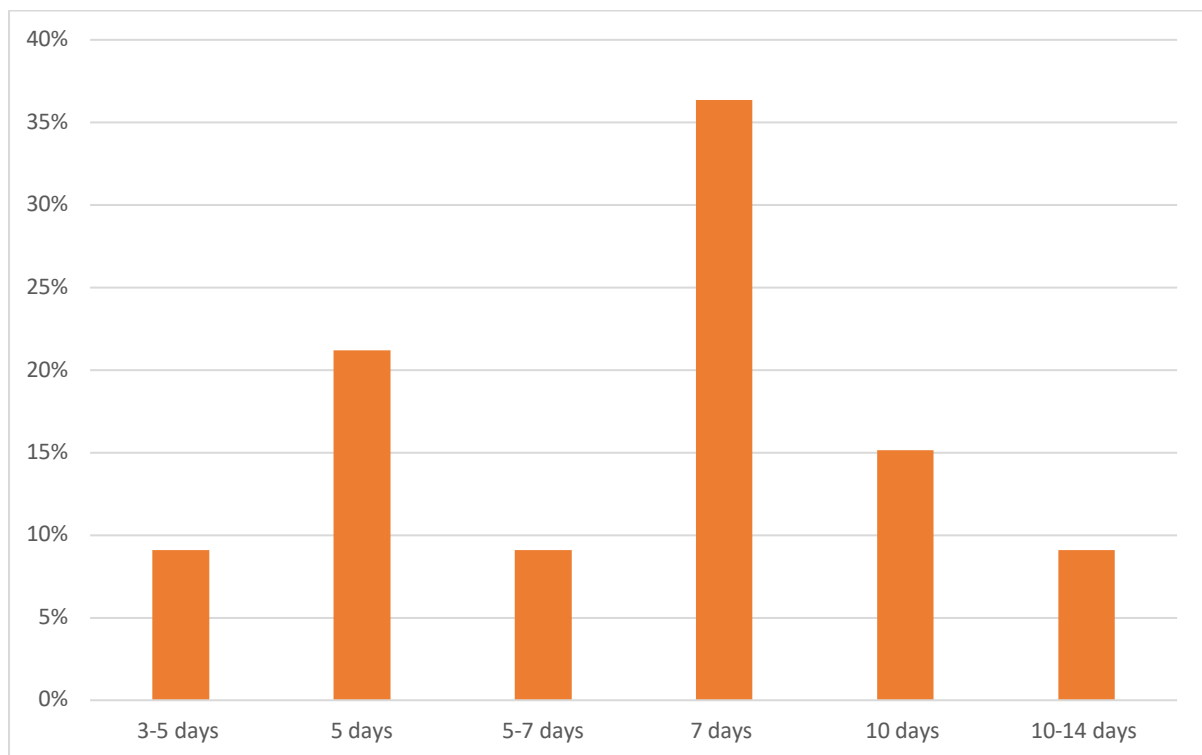


Figure 2. Antibiotic treatment duration. Percentages are based on the 74% of veterinarians prescribed antibiotics for sporadic bacterial cystitis. The recommended course duration by AMCRA is 3-5 days.

Following the guidelines

The survey revealed that of all veterinarians, 30% claimed to know the guideline by heart, while the remaining 70% indicated that they should consult AMCRA. Surprisingly, of the veterinarians claiming to know the guideline, 62% got the follow-up question about the guideline right (Fig. 3). Even more surprising is that 43% of the group that knows the guideline, prescribed a longer than recommended antibiotic treatment.

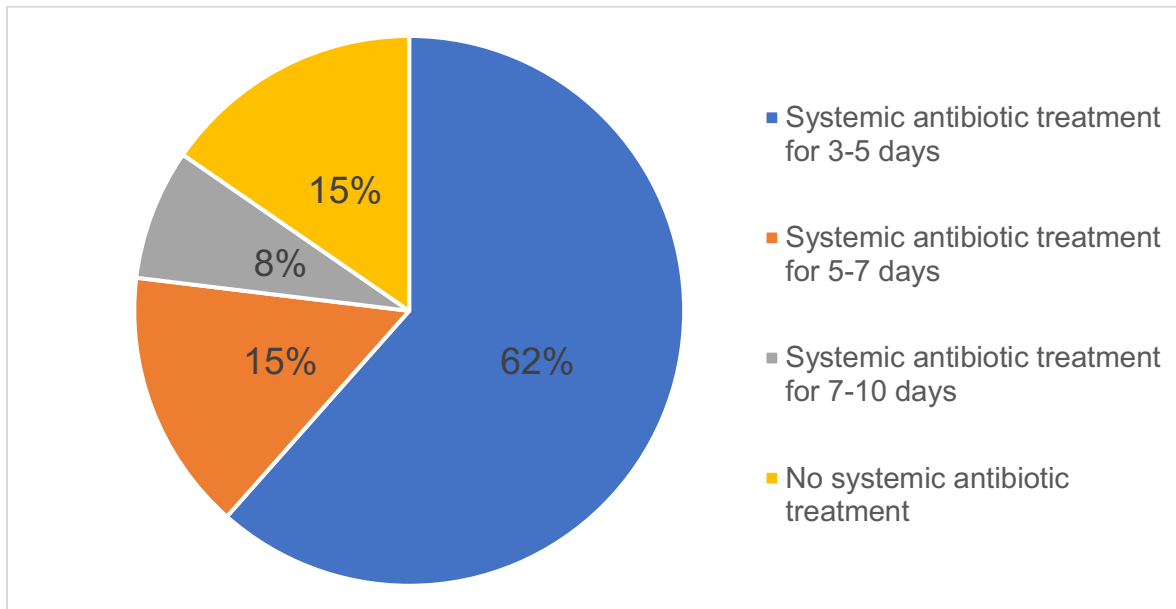


Figure 3. Answers to the follow up question what the guideline is. Percentages are based on the group of veterinarians claiming to know the guidelines by heart (i.e. 30% of all respondents).

One question was posed with the intention of eliciting response from veterinarians regarding their behavior when there was scientific evidence to support a shorter course. A shorter course would be prescribed by 79% of the responders, 3% would not because they have good experiences with longer courses and 3% would wait until the official guidelines would be adapted. The remaining 16% of respondents expressed doubt about this. The primary reason given was the perceived risk of recidivism and negative experiences with a shorter course.

The influence of graduation year

The antibiotic treatment guideline for sporadic bacterial cystitis was adjusted in 2019. Of the respondents, 47% stated to have shortened their course and 53% did not change their prescription behavior. Dividing the group into veterinarians who graduated before 2019, and in 2019 or later, a difference in prescription behavior was observed (Table 1). Among veterinarians graduated in the year that AMCRA adjusted the guideline or later, 20% followed the new guideline. In contrast, among veterinarians graduated before 2019 this was 40%. The difference between the proportions is not significant ($p=0.42$).

Table 1. The influence of graduation year on the prescribing behavior of the veterinarians.

	Follow guideline (3-5d)	Course >5 days
Graduated before 2019	40%	60%
Graduated in 2019 or later	20%	80%

Case study

A total of 26 cases of female dogs with an uncomplicated bacterial cystitis were included. The diagnosis was based on the symptoms and in 50% supported by urine-analysis and culture. In 44% an antibiogram was performed. All veterinarians prescribed antibiotics (Fig. 4).

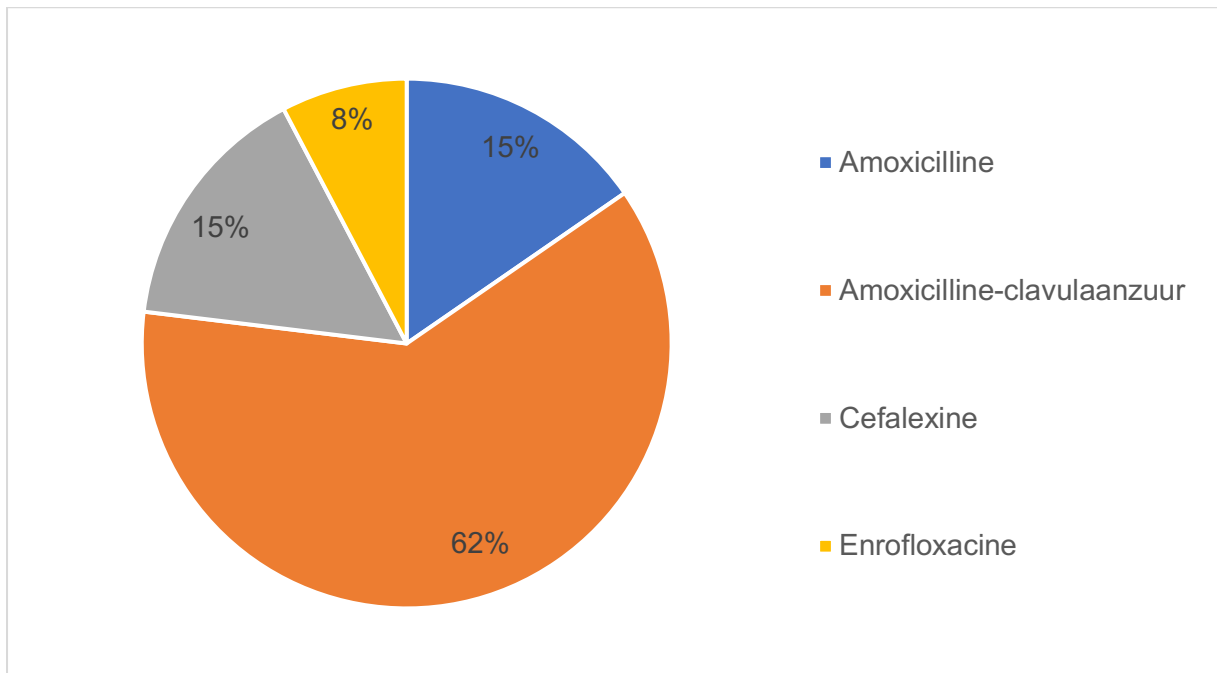


Figure 4. Specification of the prescribed antibiotics in patients with uncomplicated bacterial cystitis.

A closer examination of the treatment duration revealed that 3.8% of the patients were prescribed an antibiotic course that was in accordance with the guidelines. This indicated that 96.2% of the patients received a course that exceeded the recommended length (Fig. 5). Comparing the data from the retrospective cases and the answers from the survey, we saw that the percentage of patients from the retrospective cases receiving a correct course (i.e. three to five days) was significantly lower compared to the answers from the survey ($P=0.016$).

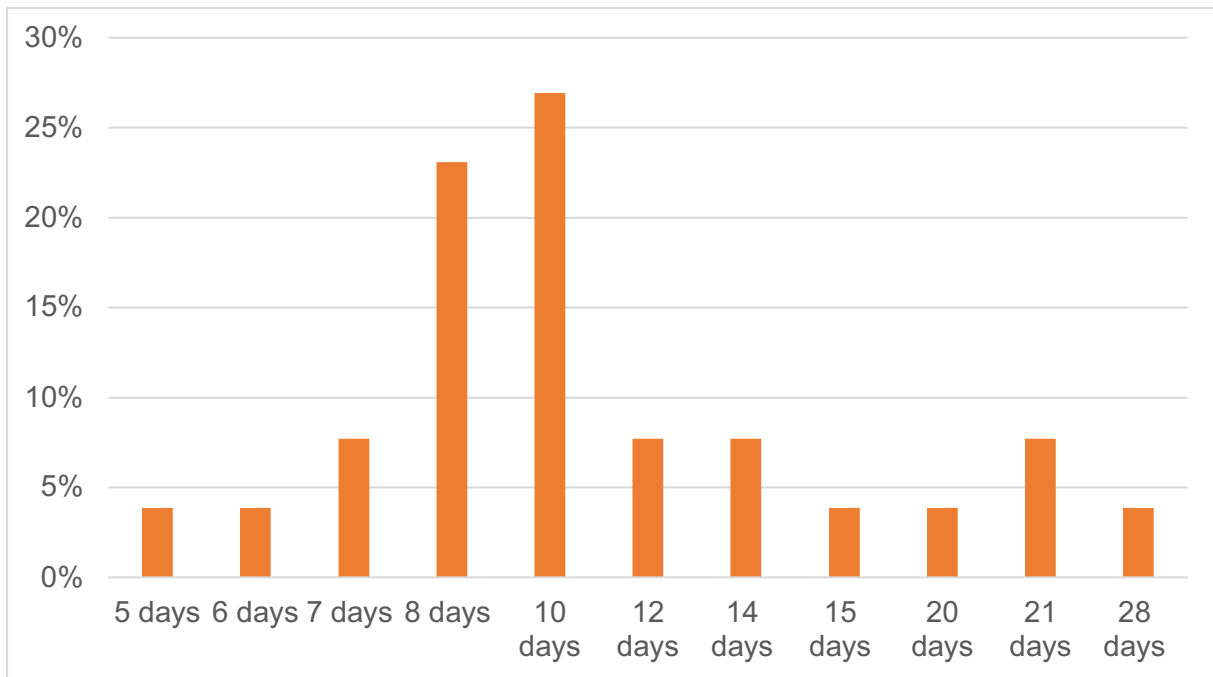


Figure 5. Antibiotic treatment duration in cases with sporadic bacterial cystitis.

Discussion

In this study, we found that a large proportion of veterinarians exceeded the recommended course duration as set by the authorities when prescribing antibiotics. Despite most veterinarians allegedly used AMCRA as a source for antimicrobial stewardship, and 82% of the respondents would alter their prescription behavior in the event of scientific research demonstrating the effectiveness of a reduced course duration, this is not reflected in the data as 3.8% of the cases were treated in accordance with the guideline.

A closer examination of the prescription behavior of sporadic bacterial cystitis provided insight into the extent of which veterinarians are up to date with the new guidelines – and whether they adjust their prescribing behavior accordingly. This data was collected via two independent methods among first-line veterinarians in Flanders. The study was conducted five years after the guideline for the treatment of cystitis was revised. The timing of this study is relevant, as it allows for an insight into the implementation of new guidelines into clinical practice over time. Since veterinarians were randomly selected, this population is an accurate representation of first line veterinarians in Flanders.

The survey revealed that 61% of the respondents claimed to follow the guidelines of AMCRA. Interestingly, we found a discrepancy between the self-assessment of following the guidelines and the responses regarding prescribing. Only 30% of the respondents prescribed a three to five day antibiotic course – in accordance with the guideline. An even bigger discrepancy was found between what veterinarians stated to prescribe in the survey versus the prescribed treatment duration in the cases. Only in 3.8% of the cases an antibiotic course was prescribed in line with the guidelines. This discrepancy was also observed in a study conducted in 2017 of Sarrazin et al. This difference, combined with the substantial proportion of veterinarians who do not prescribe according to the guidelines of AMCRA, might suggest that veterinarians are unaware of their antimicrobial use (Sarrazin et al., 2017). A centralized data collection system as implemented for farm animals, would contribute to a more reliable understanding of prescription behavior, thereby facilitating further research.

After literature review, we found that junior veterinarians are more prudent in their use of antibiotics in comparison to their older colleagues (Mateus et al., 2014) and that their mindset is more focused on AMR (King et al., 2018). Furthermore, it can be hypothesized that veterinarians who are not used to the previous guideline (i.e. the veterinarians that graduated in or after 2019) implemented the recent guideline better than their previously graduated colleagues. However, the data from this study indicated otherwise. Of the veterinarians who graduated before 2019, the proportion of those who prescribed in accordance with the guideline was double that of the more recently graduated veterinarians. This difference was however not significant. In a recent quantitative study regarding decision-making in antibiotic treatment, clinical experience and stronger communication skills were found as factors to feel more confident in withholding unnecessary antimicrobials. This has resulted in a more prudent use among senior veterinarians (Scarborough et al., 2023) – in line with the results found in this study.

Unfortunately, the response rate of the Flemish veterinarians was only 14% for sharing the cases and consequently, the limited sample size is a limitation for this study. Additionally, since the survey relies self-reported answers, recall bias is a complicating factor. The data was specified to the treatment of sporadic bacterial cystitis and cannot be directly applied to other bacterial infections. Nevertheless, interesting data was obtained about the use of AMCRA as a resource for antimicrobial stewardship, and about the willingness of first line veterinarians to adjust their prescription behavior.

Veterinarians must take their responsibility in the fight to slow down the emerge of AMR. To do so, it is essential to examine which interventions would be useful to promote behavioral change. As a starting point for this, studies such as those of Scarborough et al. or Hopman et al. can be used since they probe for reasons to prescribe unnecessary antimicrobials. Improving awareness among first line veterinarians will be an important component (Hopman et al., 2018). The treatment for sporadic bacterial cystitis continues to be a significant contributing factor to the overuse of antibiotics, as was identified in previous literature (Weese et al., 2019).

Conclusion

This study aimed to investigate whether first line veterinarians are up to date on their antibiotic prescription behavior. Surprisingly, we found a significant difference between self-reported treatment duration compared to the duration found in the retrospective case study. To provide reliable data regarding prescription behavior in companion animal veterinarians, the establishment of a centralized data collection system should be considered. Worryingly, 96.2% of the respondents prescribed an antibiotic course that exceeded the treatment duration recommended by the authorities. Therefore, improvement in the prudent use of antimicrobials in the field of small animal veterinary is essential to slow down the emergence of AMR. We can only hope that first line veterinarians, as a first point of contact for animal owners, will be aware of the crucial role they play in this global crisis.

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Appendix 1

Question 1: at which veterinary clinic do you work?

Question 2: when did you get your veterinary degree?

Question 3: regarding the prescription of antibiotics, which sources do you use to gather information?
(Multiple answers possible.)

- AMCRA
- Books
- Veterinary journals
- Summary of Product Characteristics (SPCs)
- Colleagues
- I don't need to look up any extra information
- Otherwise, namely...

Question 4: do you prescribe antibiotics to female dogs with an uncomplicated bacterial cystitis?

- Yes, namely...
- No

Question 5: for how many days do you prescribe the antibiotic course in these patients?
(This question was shown to the veterinarians who answered 'yes, namely...' on question 4)

Question 6: are you familiar with the directive of AMCRA regarding the treatment duration for an uncomplicated bacterial cystitis?

- Yes
- Not exactly, I would have to look it up

Question 7: what is the guideline of AMCRA in case of an uncomplicated bacterial cystitis?

- Systemic antibiotic treatment for 3-5 days
- Systemic antibiotic treatment for 5-7 days
- Systemic antibiotic treatment for 7-10 days
- No systemic treatment in case of an uncomplicated bacterial cystitis, only start with antibiotics in case of a recurring infection

(This question was shown to the veterinarians who answered 'yes' on question 6)

Question 8: do you follow the guidelines of AMCRA?

- Yes
- No

Question 9: did your prescription behavior regarding an uncomplicated bacterial cystitis change in the past few years?

- Yes, I prescribe shorter courses
- No, it did not change
- Yes, I prescribe longer courses

Question 10: do you notify owners that it is important to finish the course?

- Yes, I always say this, or it is written on the label
- Sometimes
- Never

Question 11: when there is scientific proof that a course can be shortened, would you change your prescription behavior?

- Yes, I would prescribe shorter courses
- I would be in doubt, because...
- I would wait until the authorities also advise this
- No, I have good experiences with the longer courses

Question 12: when the advice would be to stop the course when the patient feels better, would it be feasible in your practice to plan a control consult to decide whether the course can be discontinued?

- Yes
- No