Antibiotic therapy in dogs and cats in general practice in the United Kingdom prior to referral.

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ABSTRACT

Objectives: To describe antibiotic prescription by veterinarians in general practices in the United Kingdom (UK) prior to referral and analyse if UK antibiotic stewardship guidelines were followed.

Materials and methods: The clinical records from dogs and cats referred to the Internal Medicine and Oncology departments of two referral hospitals were retrospectively reviewed.

Results: There were 917 cases included, of which 486 (53.0%) had been prescribed antibiotics for the presentation they were subsequently referred for. Bacterial culture or cytology to guide antibiotic prescription had been performed in 43/486 (8.8%) and 9/486 cases (1.8%) respectively. In four cases, both cytology and culture were performed. For those animals who had received antibiotics, 344/486 (70.8%) prescriptions did not comply with UK antibiotic stewardship guidelines. Following investigations at a referral centre, a bacterial aetiology was found or suspected in 17.9% of the cases that received antibiotics.

Clinical significance: Use of diagnostics, including culture and cytology, to prove or determine the likelihood of a bacterial aetiology was infrequently performed prior to referral and may have contributed to over prescription of antibiotics. Encouraging veterinarians to undertake appropriate diagnostics, in combination with education around compliance with antibiotic stewardship guidelines, might reduce antibiotic prescription.

Keywords: antibiotic, antimicrobial, prescription, resistance, responsible

INTRODUCTION

Antibiotic resistance has been observed since antibiotics were first discovered. Antibiotic therapy contributes to the development of antibiotic resistance (AR) in both humans and animals (Jernberg *et al.*, 2010; Schmidt *et al.*, 2018). Any use of antibiotics exposes bacterial pathogens and commensal microbiota to a selection pressure that can result in the emergence of antibiotic resistance or, if a resistant subpopulation is present, an increase in the abundance of resistant bacteria (Weese *et al.*, 2015). This has increasingly become a problem in recent decades where use of antibiotics has accelerated the rate at which resistance has developed (Costelloe *et al.*, 2010). Broad dissemination of AR amongst different bacterial populations has resulted in treatment failures in both human and veterinary medicine (Huemer *et al.*, 2020). The concern regarding AR in veterinary medicine is further underpinned by studies investigating the nature and frequency of the contacts that occur between pets and people, which highlight the large number of opportunities that exist for the zoonotic transfer of bacteria and that have provided evidence that bacteria can be transferred in both directions (Westgarth *et al.*, 2007; Wieler *et al.*, 2011; Walther *et al.*, 2012). This interspecies transmission can further contribute to AR through a feedback loop of resistance reservoirs and the evolution of generations of increasingly resistant bacteria (Manian, 2003; Guardabassi, Loeber and Jacobson, 2004; Loeffler *et al.*, 2005; Van Balen *et al.*, 2017).

In the UK, many antibiotics are licensed for veterinary use and can only be prescribed by a veterinary surgeon (UK Stationery Office, 2013). Responsible antibiotic use can be defined as ‘an attitude to maximise therapeutic efficacy and minimise the selection of resistant microorganisms’ and should theoretically reduce the spread of antibiotic resistance (Duquette and Nuttall, 2004). The Protect and ProtectMe guidelines (BSAVA/SAMSoc, 2013, 2018) produced by the British Small Animal Veterinary Association (BSAVA) and Small Animal Medicine Society (SAMSoc) were developed to promote responsible antibacterial prescribing practises. However, it is unclear if these guidelines are widely followed in UK practice or if they have had any widespread impact on antibiotic use (Hughes *et al.*, 2012).

The aim of this study was to assess prescription of antibiotics by veterinarians in general practices in the UK prior to referral to Oncology and Internal Medicine departments for the condition the patient was subsequently referred for. A secondary aim was to analyse whether these prescriptions adhered to Protect and ProtectMe Guidelines.

MATERIALS AND METHODS

Medical records of dogs and cats who were referred to the Internal Medicine department of the hospital A between the 1st of March of 2018 and the 28th of February of 2019 and to the Internal Medicine and Oncology departments of hospital B between the 1st November 2016 and the 1st November 2017 were reviewed in a retrospective manner.

The following information was collected from each patient's medical record: signalment, clinical signs which resulted in patient referral and length of time the patient had been experiencing these clinical signs, whether or not antibiotics had been prescribed for these clinical findings, and the final or presumptive diagnosis made at the referral centres. Only information regarding antibiotics prescribed for the condition they were referred for were recorded. If an antibiotic was prescribed for the condition the patient was referred for then the following information was collected: antibiotic class, dose, route, duration and frequency of administration, whether the animal was receiving the antibiotic(s) on the day they were referred, and whether or not bacterial culture and sensitivity or cytology were performed to guide antibiotic prescription. Where an animal received multiple antibiotics, but of the same class, these were counted as different antibiotics. When the animal had received a long-acting injection of cefovecin, 14 days was assumed for duration of the antibiotic (Stegemann *et al.*, 2006; Stegemann, Sherington and Blanchflower, 2006). Where the clinical signs were reported as chronic (lasting >4 weeks), clinical records were also analysed for antibiotic use up to three months prior to referral. Animals receiving antibiotics to treat a condition independent of the reason for their referral were excluded because the final diagnosis for these conditions could not commonly be verified. Cats referred for radioiodine therapy for the treatment of hyperthyroidism at one of the centres (hospital B) were also excluded.

If the patient had been prescribed an antibiotic / antibiotics for the condition they were referred for then the patient heart rate, respiratory rate, body temperature and white blood cell count at the time of antibiotic prescription were collected and used to determine if criteria for systemic inflammatory response syndrome (SIRS) were met. When two or more (dogs) and three or more (cats) of the following criteria were met, the patient was classified as following SIRS criteria: hypothermia or fever, tachycardia or bradycardia (the latter only in cats), tachypnoea, leukocytosis, leucopenia or increased band neutrophil count in animals with a normal white blood cell count (Hauptman, Walshaw and Olivier, 1997; Brady *et al.*, 2000).

Antibiotic use was analysed using UK veterinary antibiotic guidelines (BSAVA/SAMSoc, 2013, 2018). In particular, we evaluated four ways the guidelines were not followed which could be objectively analysed: 1. evidence of underdosing, which included inferior absolute dose and insufficient frequency of administration, and was assessed against the BSAVA Small Animal Formulary 8^{th} and 9^{th} editions (Ramsey, 2014, 2018); 2. cycling antibiotics, defined as successive use of antibiotics of different classes without supportive culture and sensitivity results; 3. the inappropriate use of either fluoroquinolones or 3^{rd} and 4^{th} generation cephalosporins defined using the aforementioned guidelines when an antibiotic better aligned with prescribing guidelines is inappropriate and/or ineffective, and culture/sensitivity testing indicates that they will be effective; 4. whether antibiotics were prescribed when not indicated by aforementioned UK guidelines. We assessed antibiotic prescription in the following settings: acute vomiting (regurgitation was also included in this category), acute diarrhoea (including haemorrhagic), chronic diarrhoea (cases that received a four week treatment were excluded as antibiotic trials have been described for management of chronic diarrhoea and cases in which *Giardia spp.* infection was diagnosed and metronidazole was prescribed were also excluded as it is a recognised treatment) (Scorza V ., 2012), canine sino-nasal disease, subclinical bacteriuria, feline lower urinary tract disease, polyuria and polydipsia (unless pyogenic focus suspected), weight loss and the use of prophylactic antibiotics except for a few specific medical conditions (e.g. immunocompromised patients). If the patient met the SIRS/sepsis criteria at the time the antibiotic was prescribed, they were not classified as inappropriate.

Cases were divided into subcategories depending on body system affected (i.e. respiratory, gastrointestinal, multisystemic, hepatobiliary, endocrine, haematology/immunology, urinary/reproductive and other). Oncological cases were categorised under the major body system affected by the tumour, or where this was not possible then were classified as multisystemic.

Statistics

Descriptive statistics were used. Data were tested for normal distribution using histograms and Shapiro Wilk tests. Non-normally distributed data are presented as median and range. Chi-square tests were used to compare antibiotic prescription between species. All analyses were performed using commercial software (IBM® SPSS® v.28.0.1.1). Statistical significance was set as $P \leq 0.05$.

RESULTS

Study Population

A total of 917 animals met the inclusion criteria for the study, 265 were referred to hospital A and 652 were referred to the hospital B. Of these, 666 cases were referred to internal medicine and 251 cases to oncology.

There were 739 dogs, with 405 (54.8%) being male and 326 (44.1%) were female, of which 307 (75.8%) of males and 261 (80.0%) of females were neutered. There were 178 cats with 96 (53.9%) being male and 79 (44.4%) female, of which 89 (92.7%) of males and 74 (93.6%) of females were neutered. The sex was unknown in eight dogs and three cats. Median age of dogs at the time of referral was 7.4 years (range 1 month to 16 years) and cats was 9.3 years (range 2 months to 19 years) (Supporting information S1).

Antibiotic Prescription

There were 486 animals (53.0%), which compromised of 390/739 (52.8%) dogs and 96/178 (53.9%) cats, that had received antibiotics prior to referral for the clinical presentation they were referred for. Of the dogs who had received antibiotics, there were 223 (57.2%) males and 166 (42.6%) females, of which 163 (73.1%) of the males and 132 (79.5%) of the females were neutered. The gender was not reported in one dog. Of the cats receiving antibiotics, 52 (54.2%) were male and 43 (44.8%) were female; 43/52 (82.7%) of males and 40/43 (93.0%) of females were neutered. The gender was not reported in one cat. The median age of the dogs who received antibiotics was 8 years (range 1 to 16 years) and for cats was 8 years (range 2 months to 19 years).

Three hundred and forty seven cases had been prescribed one antibiotic class. Two different antibiotic classes had been prescribed for 120/486 animals (24.7%), whilst 16 (3.3%) had received three different antibiotic classes, three (0.6%) had received four antibiotic classes and one animal received five different antibiotic classes. One hundred and sixty animals (32.9%) were still receiving antibiotics at the time of referral.

Table 1 describes antibiotic classes prescribed. The antibiotic classes most commonly prescribed in dogs were penicillins in 279/390 (71.5%) cases and nitroimidazoles (ie. metronidazole) in 100/390 (25.6%) cases. For cats, the most common classes prescribed were penicillins in 47/96 (49.0%) cases and third generation cephalosporins in 32/96 (33.3%). When antibiotics were prescribed, cats were significantly less likely to receive a penicillin antibiotic (X^2 (1, N = 486) = 17.8, p <0.001) and more likely to be prescribed a 3rd generation cephalosporin compared with dogs (X^2 (1, N =486) = 79.5, p<0.001). The only third generation cephalosporin that was prescribed for both dogs and cats was cefovecin.

The data for the combination of antibiotic classes prescribed is presented in Figure 1 and 2.The most commonly prescribed combination of antibiotics was a nitroimidazole and a penicillin in both dogs (40/390; 10.2%) and cats (6/96; 6.3%). In dogs, the second most common combination of antibiotics included a penicillin and a fluoroquinolone (9/390; 2.3%) and a penicillin and a lincosamide (9/390; 2.3%), whilst in cats a penicillin and a 3rd generation cephalosporin was the second most common combination (5/96; 5.2%).

The data for the antibiotic classes prescribed for each body system is presented in Figure 3. Penicillins were the most commonly prescribed antibiotic class for all body systems (endocrine 10/46; 21.7%, haematological/immunological 7/31; 22.6%, hepatobiliary 24/69; 34.8%, multisystemic 108/320; 33.8%, respiratory 49/108; 45.4% and urinary/reproductive 43/86; 50%) apart from the gastrointestinal body system where it was nitroimidazoles (67/170; 39.4%). When lincosamides or second and third generation cephalosporines were prescribed, they were most commonly prescribed for multisystemic disease (lincosamides 17/320; 5.3%, second generation cephalosporines 15/320; 4.7% and third generation cephalosporines 19/320; 5.9%) (Supporting information S2).

Use of culture and sensitivity and/or cytology to guide antibiotic prescription

A bacterial culture and sensitivity had been performed in 43/486 (8.8%) animals that had been prescribed antibiotics prior to referral. In 10/43 (23.3%), the antibiotic prescription was considered inappropriate on the basis that results were obtained from nasal swabs, which typically isolates microorganisms representative of colonisation rather than true infection (Meler, Dunn and Lecuyer, 2008).

Nine (1.9%) patients underwent cytology testing to guide antibiotic prescription. The antibiotic prescription was considered questionable in one dog where extracellular bacteria were seen in an otherwise inactive urine sediment and in one cat where bacteria likely representing normal flora were seen in an upper respiratory secretion. In four cases, both cytology and culture were performed.

SIRS/sepsis criteria

Out of 390 dogs that had received antibiotics, 85 dogs (21.8%) had data in the clinical records available to assess for SIRS criteria at the time of antibiotics prescription. Of these, 10 (11.8) dogs had all four criteria available (i.e., heart rate, respiratory rate, temperature and haematology), 38 (44.7%) dogs had three criteria available and 37 (43.5%) had two criteria available. Of the 10 dogs with four criteria available, eight were classified as following SIRS criteria. Ten of 38 dogs with three criteria available were classified as following SIRS criteria and six of 37 dogs with two criteria available were classified as following SIRS criteria.

Out of 96 cats that received antibiotics, 9 (9.4%) cats had data in the clinical records available to assess for SIRS at the time of antibiotic prescription. One cat had all four criteria available and 8 cats had three criteria available. The cat with the four criteria available was classified as following SIRS criteria and six of nine cats with 3 criteria available were classified as following SIRS criteria.

Therefore, only 27/94 (14.3%) animals with enough data available to assess SIRS met the criteria for SIRS at the time they had been prescribed an antibiotic.

Antibiotic guidelines

When considering Protect/ProtectME guidelines, 344/486 (70.8%) cases did not have antibiotic prescription in line with these guidelines in one way only (i.e. underdosing, cycling antibiotics, inappropriate prescription of fluoroquinolones or third generation cephalosporins and use of antibiotics for clinical signs that were recommended against antibiotic use by the guidelines.)

One hundred and eleven (47.8%) cases did not adhere with the guidelines in two different ways, 31 (17.7%) cases in three different ways and 8 (3.4%) cases in the four ways assessed. Underdosing was recorded in 131/486 (26.9%) cases. Cycling antibiotics occurred in 97/467 (i.e. 20.8%, 19 patients were prescribed two antibiotics from the start of their treatment), following apparent failure of a first antibiotic, cases were prescribed a second antibiotic without supportive culture and sensitivity results.). There were 91/486 (18.7%) cases that were prescribed a fluoroquinolone or third generation cephalosporin, and nappropriate prescription of these two classes of antibiotics occurred in 81/91 (89.0%) cases.A culture and sensitivity test had been performed in 1/91 cases that were prescribed these class of antibiotics.

There were 232/486 (47.7%) cases that had been prescribed antibiotics for clinical signs where antibiotics are not recommended by the Protect/ProtectME guidelines.

Of the patients who received a prior antibiotics as indicated by UK guidelines, only clinical variables met SIRS/sepsis criteria, 13/20 dogs and 3/7 cats who met these criteria subsequently received antibiotics which did not adhere to UK guidelines (Supporting information S3, S4 and S5).

Bacterial infection documented

After investigations within a referral centre setting, a bacterial aetiology was found in 55/486 (11.3%) cases that received antibiotics, and was suspected in a further 32 (6.6%) cases. Therefore, a bacterial aetiology was found or suspected in 17.9% of the cases that received antibiotics. For one cat included here, *Helicobacter spp* was diagnosed within gastric biopsy samples.

DISCUSSION

Our data demonstrates that substantial improvement on adherence to antibiotic guidelines in general practice in the UK can be made as in 70.9% of the cases referred to internal medicine or oncology the guidelines were not followed. It also demonstrates over-prescription of antibiotics and infrequent use of appropriate tools to diagnose bacterial infection such as culture or cytology.

Three general approaches have been recommended to help limit antibiotic resistance: a) preventing disease occurrence, b) reducing overall antibiotic use and c) improved antibiotic use (Weese *et al.*, 2015).

Setting aside prevention of disease, which was not a focus of our study, and focusing on the approach of reducing overall antibiotic use, our data demonstrated an over-prescription of antibiotics in general practice in the UK relative to indication. This study reports that 17.9% of the cases who had received antibiotics and were referred to internal medicine and oncology services ultimately had a bacterial aetiology confirmed or suspected at the referral centre. In an attempt to limit an underestimation of cases with a bacterial aetiology, we included both confirmed and suspected bacterial aetiology as categories for analysis.

Various drivers have been attributed to the over-prescription of antibiotics in veterinary practice. This includes client factors such as perceived client satisfaction, commercial pressures to retain clients and the symbolic value of giving treatment (Smith *et al.*, 2018). Interestingly however, this was not borne out in pet owner surveys, where pet owners reported a perception of over-prescription by veterinarians (Smith *et al.*, 2018). Additional contributing factors to consider may include time pressures and clinical and financial resources available to allow a definitive diagnosis.

Focusing on the approach to limit AR of improved antibiotic use, the Protect / ProtectMe Guidelines attempt to guide veterinarians when antibiotics might be appropriate, and thereby reduce unnecessary prescription. Our data demonstrates poor adherence to antibiotic guidelines.. The most common way in which the Protect/ProtectMe guidelines were not followed was the prescription of antibiotics for clinical signs for which the guidelines were specifically advising veterinarians against, which happened in 47.7% of the cases that received antibiotics. Of those, the most common were uncomplicated vomiting and/or diarrhoea. In addition to breaking from the Protect / ProtectMe guidelines, this also goes against additional antibiotic use guidelines, where recommendations around managing enteropathogenic bacterial infections recommend reserving antibiotics for patients demonstrating signs of sepsis (Marks *et al.*, 2011). Furthermore, although a recent study suggests that metronidazole can shorten duration of acute non-specific diarrhoea in some dogs (Langlois, Koenigshof and Mani, 2020), multiple other veterinary studies indicate a limited benefit (Jergens *et al.*, 2010; Shmalberg *et al.*, 2019; Werner *et al.*, 2020, Busch *et al.*, 2015)). For chronic enteropathies, current UK antibiotic guidelines consider appropriate a four-week trial of antibiotics for determining if the clinical presentation is antibiotic-responsive. However, a recent publication proposes antibiotic use is reserved until other therapeutic trials are proven unsuccessful, including diet/pre-probiotics or immunosuppressive drugs (Cerquetella *et al.*, 2020).

In our cohort, metronidazole was commonly prescribed to manage both acute and chronic gastrointestinal disorders, similar to data collected across Europe (Hughes *et al.*, 2012). Whilst metronidazole is a popular choice to manage *Clostridial sp.* in people, the role of *Clostridial sp.* in canine diarrhoea syndromes remains uncertain (Busch *et al.*, 2015). Metronidazole also disrupts the normal canine microbial flora, and is associated with an increased risk of becoming a carrier for multi-drug-resistant *Escherichia coli* (Gibson *et al.*, 2011; Igarashi *et al.*, 2014). Further, it may increase the risk of bacterial translocation, which has been shown in laboratory mice. (Wells *et al.*, 1987).

Another clinical sign in which antibiotics were frequently prescribed but which contradicted Protect/ProtectMe guidance against their use was feline lower urinary tract signs. Similar to recommendations within the ISCAID guidelines (Weese *et al.*, 2011, 2019), Protect/ProtectMe guidelines state that bacterial culture and susceptibility testing should be performed in all cases of suspected bacterial cystitis. However, an update to those guidelines (Weese *et al.*, 2019), was not available for use at the time of the study, with older guidelines (Weese *et al.*, 2011) conflicting with Protect / ProtectMe guidance in that they supported empiric antibiotic therapy while awaiting culture and susceptibility results to relieve patient discomfort. This could have been one reason why antibiotics were prescribed in this setting. Current recommendations are to confirm a diagnosis of bacterial cystitis, by culture, in all feline patients due to the low likelihood of bacterial cystitis in cats. Further to this, clinical signs of bacterial cystitis are frequently a result of inflammation and there is some evidence from humans that analgesics alone may be as effective as antibiotics in uncomplicated cases (Bleidorn *et al.*, 2016).

Both polyuria/polydipsia and canine sino-nasal disease were also associated with poor adherence to Protect / ProtectMe guidelines. Multiple aetiologies can result in polyuria and polydipsia in dogs and cats, with antibiotics only necessary where a septic focus is identified or strongly suspected. Primary bacterial rhinitis is an uncommon entity in dogs, with bacterial rhinitis more likely to occur as a sequela to inhaled foreign bodies or as a consequence of loss of turbinates resulting from mycotic disease, or trauma. In these cases, antibiotics might improve clinical signs but rarely permanently (Windsor *et al.*, 2006).

In human medicine sepsis guidelines, antibiotics are recommended within one hour of recognition in patients with septic shock or high likelihood/confirmed of sepsis, given the strong association of antibiotic timing and mortality (Evans *et al.*, 2021). SIRS/sepsis criteria were assessed as a possible reason why antibiotics may have been prescribed in these patients in which assessing clinical signs alone, the prescription was considered inappropriate. Only 6.9% of the population met the criteria for SIRS/sepsis at the time they were prescribed with antibiotics. However, only 85 (21.8%) dogs and 9 (9.4%) cats had criteria available at the time of antibiotic prescription to make some assessment for SIRS, with the vast majority not having complete criteria available. Of those, 36.2% of the animals met the SIRS criteria, although a significant proportion of these were classified based upon 2 or 3 criteria alone. It is difficult to make robust conclusions around the incidence of SIRS in this cohort given the vast majority of cases prescribed antibiotics had insufficient information available to make an assessment at all. This could reflect those parameters were normal but were not documented, were not assessed due to short consultation durations in general practise in the UK, or a lack of emphasis regarding the importance of those factors in decision making around antibiotic use.

Failure to confirm a bacterial aetiology and evaluate antibiotic susceptibilities leads to the misuse of antibiotics, and does not allow veterinarians to make adequate choices around appropriate prescription (EMA, 2015; The Veterinary Medicines, 2015; Weese *et al.*, 2015). The data from our study demonstrates that antibiotic prescription was based on results of culture and sensitivity in only 8.8% of cases, whilst cytology was used in only 1.8% of cases, with only a very small number of cases having both. This is similar to data reported elsewhere, where only approximately half of veterinarians surveyed considered bacterial culture and sensitivity as important prior to prescribing antibiotics with fewer (30%) considering cytology useful (Hughes *et al.*, 2012).

Prescription of beta-lactams was common in our study, similar to previous publications from the UK (Mateus *et al.*, 2011; Radford *et al.*, 2011). The most common prescribed beta-lactam were penicillins, which were prescribed in 71.5% of dogs and 49.0% of cats. Nitroimidazoles (i.e. metronidazole) was the second most commonly prescribed antibiotic class in dogs, higher than in other reports (Mateus *et al.*, 2011; Radford *et al.*, 2011). This difference could be attributed to a population bias of patients referred to Internal Medicine, where gastrointestinal signs may be more common than within the general population and metronidazole is commonly prescribed in cases with diarrhoea as previously mentioned (Hughes *et al.*, 2012). In cats, third generation cephalosporins were the second most used antibiotic, more specifically cefovecin. This antibiotic choice was significantly different between cats and dogs. This has previously been reported in the UK and Europe after authorisation of cefovecin, and likely reflects ease-of-use of long-acting injections in a species frequently non-compliant with oral therapeutics (Levy, 1998; Mateus *et al.*, 2011; Burke *et al.*, 2017). Cost associated with cefovecin administration may also negatively impacts use in dogs (Mateus *et al.*, 2011).

Fluoroquinolones or third generation cephalosporins were inappropriately prescribed in 89.0% of the cases receiving these classes of antibiotics, as culture and sensitivity had not been performed, and/or as other agents could have been used (Collignon *et al.*, 2016). The WHO classifies these antibiotic classes as highest priority critically important antibiotics and it has even been suggested that use of these antibiotics should be banned in animals to preserve their effectiveness in human medicine (Hughes *et al.*, 2012; Collignon *et al.*, 2016). However, there are concerns that a complete ban in veterinary medicine could be detrimental to animal health and welfare (Hughes *et al.*, 2012). UK antibiotic guidelines recommend use only when an antibiotic better aligned with prescribing guidelines is inappropriate and/or ineffective, and culture/sensitivity testing indicates that they will be effective.

Underdosing of antibiotics was documented in 26.9% of the cases included in our study, and this practice could result in subinhibitory concentrations and resistance (Choe *et al.*, 2000; Gillespie *et al.*, 2005; Ungemach, Müller-Bahrdt and Abraham, 2006). Reasons for underdosing were not always apparent. Miscalculations or rounding dosages to the nearest tablet size are considered possibilities.

Our study has several limitations that reflect its retrospective nature, a referral population bias, and within that, limitation to Oncology and Internal Medicine disciplines. As is frequently the case with retrospective studies, data was not always complete regarding clinical signs, antibiotic prescription, and physical examination. We included cases where a bacterial aetiology was "suspected" as one of the differential diagnosis based upon comment in the referral communications, but it is possible that differentials associated with suspected bacterial infection were not mentioned.

On its own, a referral population could be expected to bias data through increased case complexity and perhaps a higher frequency of antibiotic use. Further restriction to only Internal Medicine and Oncology cases could theoretically be expected to increase the overall antibiotic prescription frequency in this cohort, compared to other disciplines if they were also included. Discipline restriction could also have impacted choices around antibiotic classes prescribed, for example exclusion of Dermatology might be expected to comparatively reduce prescription of cephalosporins.

We decided to investigate a referral population as they underwent extensive referral investigations so we considered that that appropriateness of the use of antibiotics could be addressed better than in cases without it. However, our findings may under-represent antibiotic prescriptions in a general practice setting, as cases that improved as a result of, or spontaneously irrespective of antibiotic prescription, are unlikely to be referred.

Lastly, between the two referral hospitals included, different timeframes were assessed, however this is considered unlikely to cause a significant shift in prescription patterns. This timeframe did cover an update on the guidelines in November 2018, however we limited the recommendations assessed and included to those present in both versions.

Specific UK guidelines were assessed, and it is possible that veterinarians were following a different antibiotic guideline with conflicting recommendations. Apart from the discussed previously regarding feline lower urinary tract disease and chronic diarrhoea already mentioned, no other conflicting recommendations were found.

Given roles in managing domestic animals with close human bonds, as well as roles within the human food chain, veterinarians have an integral role in promoting responsible use of antibiotics. It has been estimated that without proactive solutions to slow rising antibiotic resistance, or discovery of new antibiotics, that 10 million lives a year will be at risk by 2050 (Neill, 2014) We were not able, and did not set out, to evaluate veterinarians knowledge or understanding of existing antibiotic stewardship guidelines, or to determine what barriers might lead to non-compliance. However, our data identifies several aspects worthy of further exploration and investment in improving education around appropriate diagnostics, antibiotic class and dosage choices, thereby leading to improved compliance within antibiotic stewardship guidelines and more responsible use of antibiotics.

In conclusion, over prescription of antibiotics, poor adherence to UK antibiotic guidelines and infrequent use of diagnostics such as culture and cytology to guide antibiotic use was observed.

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Antibiotic therapy in dogs and cats in general practice in the United Kingdom prior to referral.

ABSTRACT

Objectives: To describe antibiotic prescription by veterinarians in general practices in the United Kingdom (UK) prior to referral and analyse if UK antibiotic stewardship guidelines were followed.

Materials and methods: The clinical records from dogs and cats referred to the Internal Medicine and Oncology departments of two referral hospitals were retrospectively reviewed.

Results: There were 917 cases included, of which 486 (53.0%) had been prescribed antibiotics for the presentation they were subsequently referred for. Bacterial culture or cytology to guide antibiotic prescription had been performed in 43/486 (8.8%) and 9/486 cases (1.8%) respectively. In four cases, both cytology and culture were performed. For those animals who had received antibiotics, 344/486 (70.8%) prescriptions did not comply with ~~local~~ UK antibiotic stewardship guidelines. Following investigations at a referral centre, a bacterial aetiology was found or suspected in 17.9~~24.1~~~~9.5~~% of the cases that received antibiotics.

Clinical significance: Use of diagnostics, including culture and cytology, to prove or determine the likelihood of a bacterial aetiology was infrequently performed prior to referral and may have contributed to over prescription of antibiotics. Encouraging veterinarians to undertake appropriate diagnostics, in combination with education around compliance with antibiotic stewardship guidelines, might reduce antibiotic prescription.

Keywords: antibiotic, antimicrobial, prescription, resistance, responsible

INTRODUCTION

Antibiotic resistance has been observed since antibiotics were first discovered. Antibiotic therapy contributes to the development of antibiotic resistance (AR) in both humans and animals (Jernberg *et al.*, 2010; Schmidt *et al.*, 2018). Any use of antibiotics exposes bacterial pathogens and commensal microbiota to a selection pressure that can result in the emergence of antibiotic resistance or, if a resistant subpopulation is present, an increase in the abundance of resistant bacteria (Weese *et al.*, 2015). This has increasingly become a problem in recent decades where use of antibiotics has accelerated the rate at which resistance has developed (Costelloe *et al.*, 2010). Broad dissemination of AR amongst different bacterial populations has resulted in treatment failures in both human and veterinary medicine (Huemer *et al.*, 2020). The concern regarding AR in veterinary medicine is further underpinned by studies investigating the nature and frequency of the contacts that occur between pets and people, which highlight the large number of opportunities that exist for the zoonotic transfer of bacteria and that have provided evidence that bacteria can be transferred in both directions (Westgarth *et al.*, 2007; Wieler *et al.*, 2011; Walther *et al.*, 2012). This interspecies transmission can further contribute to AR through a feedback loop of resistance reservoirs and the evolution of generations of increasingly resistant bacteria (Manian, 2003; Guardabassi, Loeber and Jacobson, 2004; Loeffler *et al.*, 2005; Van Balen *et al.*, 2017).

In the UK, many antibiotics are licensed for veterinary use and can only be prescribed by a veterinary surgeon (UK Stationery Office, 2013). Responsible antibiotic use can be defined as 'an attitude to maximise therapeutic efficacy and minimise the selection of resistant microorganisms' and should theoretically reduce the spread of antibiotic resistance (Duquette and Nuttall, 2004). The Protect and ProtectMe guidelines (BSAVA/SAMSoc, 2013, 2018) produced by the British Small Animal Veterinary Association (BSAVA) and Small Animal Medicine Society (SAMSoc) were developed to promote responsible antibacterial prescribing practises. However, it is unclear if these guidelines are widely followed in UK practice or if they have had any widespread impact on antibiotic use (Hughes *et al.*, 2012).

The aim of this study was to assess prescription of antibiotics by veterinarians in general practices in the UK prior to referral to Oncology and Internal Medicine departments for the condition the patient was subsequently referred for. A secondary aim was to analyse whether these prescriptions adhered to Protect and ProtectMe Guidelines.

MATERIALS AND METHODS

Medical records of dogs and cats who were referred to the Internal Medicine department of the hospital A between the 1st of March of 2018 and the 28th of February of 2019 and to the Internal Medicine and Oncology departments of hospital B between the 1st November 2016 and the 1st November 2017 were reviewed in a retrospective manner.

The following information was collected from each patient's medical record: signalment, clinical signs which resulted in patient referral and length of time the patient had been experiencing these clinical signs, whether or not antibiotics had been prescribed for these clinical findings, and the final or presumptive diagnosis made at the referral centres. Only information regarding antibiotics prescribed for the condition they were referred for were recorded. If an antibiotic was prescribed for the condition the patient was referred for then the following information was collected: antibiotic class, dose, route, duration and frequency of administration, whether the animal was receiving the antibiotic(s) on the day they were referred, and whether or not bacterial culture and sensitivity or cytology were performed to guide antibiotic prescription. Where an animal received multiple antibiotics, but of the same class, these were counted as different antibiotics. When the animal had received a long-acting injection of cefovecin, 14 days was assumed for duration of the antibiotic (Stegemann *et al.*, 2006; Stegemann, Sherington and Blanchflower, 2006). Where the clinical signs were reported as chronic (lasting >4 weeks), clinical records were also analysed for antibiotic use up to three months prior to referral. Animals receiving antibiotics to treat a condition independent of the reason for their referral were excluded because the final diagnosis for these conditions could not commonly be verified. Cats referred for radioiodine therapy for the treatment of hyperthyroidism at one of the centres (hospital B) were also excluded.

If the patient had been prescribed an antibiotic / antibiotics for the condition they were referred for then the patient heart rate, respiratory rate, body temperature and white blood cell count at the time of antibiotic prescription were collected and used to determine if criteria for systemic inflammatory response syndrome (SIRS) were met. When two or more (dogs) and three or more (cats) of the following criteria were met, the patient was classified as following SIRS criteria: hypothermia or fever, tachycardia or bradycardia (the latter only in cats), tachypnoea, leukocytosis, leucopenia or increased band neutrophil count in animals with a normal white blood cell count (Hauptman, Walshaw and Olivier, 1997; Brady *et al.*, 2000).

Antibiotic use was analysed ~~against~~ using UK veterinary antibiotic guidelines (BSAVA/SAMSoc, 2013, 2018). In particular, we evaluated four ways the guidelines were not followed which ~~recommendations which~~ could be objectively analysed: 1. evidence of underdosing, which included inferior absolute dose and insufficient frequency of administration, and was assessed against the BSAVA Small Animal Formulary 8th and 9th editions (Ramsey, 2014, 2018); 2. ~~or~~ cycling ~~through various~~ antibiotics, defined as successive use of antibiotics of different classes without supportive culture and sensitivity results; 3. the inappropriate use of either fluoroquinolones or 3rd and 4th generation cephalosporins defined using the aforementioned guidelines ~~without bacterial culture and sensitivity results.~~when an antibiotic better aligned with prescribing guidelines is inappropriate and/or ineffective, and culture/sensitivity testing indicates that they will be effective; 4. ~~Evidence of underdosing included inferior absolute dose, or insufficient frequency of administration, and was assessed against the BSAVA Small~~

~~Animal Formulary 8th and 9th editions (Ramsey, 2014, 2018).~~whether antibiotics were prescribed when ~~defined as~~ not indicated by aforementioned ~~local~~ UK guidelines. ~~Specifically~~ ~~w~~We assessed antibiotic prescription in the following settings: acute vomiting (regurgitation was also included in this category), acute diarrhoea (including haemorrhagic), chronic diarrhoea (cases that received a four week treatment were excluded as antibiotic trials have been described for management of chronic diarrhoea and cases in which *Giardia spp.* infection was diagnosed and metronidazole was prescribed were also excluded as it is a recognised treatment) (Scorza V ., 2012), canine sino-nasal disease, subclinical bacteriuria, feline lower urinary tract disease, polyuria and polydipsia (unless pyogenic focus suspected), weight loss and the use of prophylactic antibiotics except for a few specific medical conditions (e.g. immunocompromised patients). If the patient met the SIRS/sepsis criteria at the time the antibiotic was prescribed, they were not classified as inappropriate.

Cases were divided into subcategories depending on body system affected (i.e. respiratory, gastrointestinal, multisystemic, hepatobiliary, endocrine, haematology/immunology, urinary/reproductive and other). Oncological cases were categorised under the major body system affected by the tumour, or where this was not possible then were classified as multisystemic.

Statistics

Descriptive statistics were used. Data were tested for normal distribution using histograms and Shapiro Wilk tests. Non-normally distributed data are presented as median and range. Chi-square tests were used to compare antibiotic prescription between species. All analyses were performed using commercial software (IBM® SPSS® v.28.0.1.1). Statistical significance was set as $P \leq 0.05$.

[illegible]

RESULTS

Study Population

A total of 917 animals met the inclusion criteria for the study, 265 were referred to hospital A and 652 were referred to the hospital B. Of these, 666 cases were referred to internal medicine and 251 cases to oncology.

There were 739 dogs, with 405 (54.8%) being male and 326 (44.1%) were female, of which 307 (75.8%) of males and 261 (80.0%) of females were neutered. There were 178 cats with 96 (53.9%) being male and 79 (44.4%) female, of which 89 (92.7%) of males and 74 (93.6%) of females were neutered. The sex was unknown in eight dogs and three cats. Median age of dogs at the time of referral was 7.4 years (range 1 month to 16 years) and cats was 9.3 years (range 2 months to 19 years) (Supporting information S1).

Antibiotic Prescription

There were 486 animals (53.0%), which compromised of 390/739 (52.8%) dogs and 96/178 (53.9%) cats, that had received antibiotics prior to referral for the clinical presentation they were referred for. ~~, which comprised of 390 dogs and 96 cats.~~ Of the dogs who had received antibiotics, there were 223 (57.2%) males and 166 (42.6%) females, of which ~~285~~ 163 (73.1%) of the males and ~~319~~ 132 (79.5%) of the females were neutered. The gender was not reported in one dog. Of the cats receiving antibiotics, 52 (54.2~~3.6~~%) were male and 43 (44.8~~3~~%) were female; 43/52 (82.7%) of males and 40/43 (93.0~~1~~%) of females were neutered. The gender was not reported in one cat. The median age of the dogs who received antibiotics was 8 years (range 1 to 16 years) and for cats was 8 years (range 2 months to 19 years).

Three hundred and forty seven cases had been prescribed one antibiotic class. Two different antibiotic classes had been prescribed for ~~133~~120/486 animals (~~27.4~~24.7%), whilst ~~21~~ 16 (3.3%) had received three different antibiotic classes, three~~3~~ (0.6%) had received four antibiotic classes and one animal received five different antibiotic classes. One hundred and sixty animals (32.9%) were still receiving antibiotics at the time of referral.

Table 1 describes antibiotic classes prescribed. The antibiotic classes most commonly prescribed in dogs were penicillins in 279/390 (71.5%) cases and nitroimidazoles (ie. metronidazole) in 100/390 (25.6%) cases. For cats, the most common classes prescribed were penicillins in 47/96 (49.0%) cases and third generation cephalosporins in 32/96 (33.3%). When antibiotics were prescribed, cats were significantly less likely to receive a penicillin antibiotic (X^2 (1, N = 486) = 17.8, p <0.001) and more likely to be prescribed a 3rd generation cephalosporin compared with dogs (X^2 (1, N =486) = 79.5, p<0.001). The only third generation cephalosporin that was prescribed for both dogs and cats was cefovecin.

The data for the combination of antibiotic classes prescribed is presented in Figure 1 and 2. The most commonly prescribed combination of antibiotics was a nitroimidazole and a penicillin in both dogs (40/390; 10.2%) and cats (6/96; 6.32%). In dogs, the second most common combination of antibiotics included a penicillin and a fluoroquinolone (9/390; 2.3%) and a penicillin and a lincosamide (9/390; 2.3%), whilst in cats a penicillin and a 3rd generation cephalosporin was the second most common combination (5/96; 5.2%).

The data for the antibiotic classes prescribed for each body system is presented in Figure 3. Penicillins were the most commonly prescribed antibiotic class for all body systems (endocrine 10/46; 21.7%, haematological/immunological 7/31; 22.6%, hepatobiliary 24/69; 34.8%, multisystemic 108/320; 33.8%, respiratory 49/108; 45.4% and urinary/reproductive 43/86; 50%) apart from the gastrointestinal body system where it was nitroimidazoles (67/170; 39.4%). When lincosamides or second and third generation cephalosporines were prescribed, they were most commonly prescribed for multisystemic disease (lincosamides 17/320; 5.3%, second generation cephalosporines 15/320; 4.7% and third generation cephalosporines 19/320; 5.9%) (Supporting information S2).

Use of culture and sensitivity and/or cytology to guide antibiotic prescription

A bacterial culture and sensitivity had been performed in 43/486 (8.8%) animals that had been prescribed antibiotics prior to referral. In 10/43 (23.3%), the antibiotic prescription was considered inappropriate on the basis that results were obtained from nasal swabs, which typically isolates microorganisms representative of colonisation rather than true infection (Meler, Dunn and Lecuyer, 2008).

Nine (1.9%) patients underwent cytology testing to guide antibiotic prescription. The antibiotic prescription was considered questionable in one dog where extracellular bacteria were seen in an otherwise inactive urine sediment and in one cat where bacteria likely representing normal flora were seen in an upper respiratory secretion. In four cases, both cytology and culture were performed.

SIRS/sepsis criteria

Out of 390 dogs that had received antibiotics, 85 dogs (21.8%) had data in the clinical records available to assess for SIRS criteria at the time of antibiotics prescription. Of these, 10 (11.8) dogs had all ~~4~~ four criteria available (i.e., heart rate, respiratory rate, temperature and haematology), 38 (44.7%) dogs had ~~3~~ three criteria available and 37 (43.5%) had ~~2~~ two criteria available. Of the 10 dogs with ~~4~~ four criteria available, ~~8~~ eight were classified as following SIRS criteria. ~~Fourteen~~ Ten of 38 dogs with ~~3~~ three criteria available were classified as following SIRS criteria and ~~10~~ six of 37 dogs with ~~2~~ two criteria available were classified as following SIRS criteria.

Out of 96 cats that received antibiotics, 9 (9.4%) cats had data in the clinical records available to assess for SIRS at the time of antibiotic prescription. One cat had all ~~4~~ four criteria available and 8 cats had ~~3~~ three criteria available. The cat with the four criteria available was classified as following SIRS criteria and ~~one~~ six ~~out~~ of ~~9~~ nine cats with 3 criteria available ~~was~~ were classified as following SIRS criteria.

Therefore, only ~~34~~27/94 (~~36.2~~14.3%) animals with enough data available to assess SIRS met the criteria for SIRS at the time they had been prescribed an antibiotic.

~~Local a~~Antibiotic guidelines

When considering Protect/ProtectME guidelines, 344/486 (70.8%) cases did not have antibiotic prescription in line with these guidelines in one way only (i.e. underdosing, cycling antibiotics, inappropriate prescription of fluoroquinolones or third generation cephalosporins and use of antibiotics for clinical signs that were recommended against antibiotic use by the guidelines.)~~.~~

One hundred and eleven (47.8%) cases did not adhere with the guidelines in two different ways, 31 (17.7%) cases in three different ways and 8 (3.4%) cases in the four ways assessed. ~~(i.e. underdosing, cycling antibiotics, inappropriate prescription of fluoroquinolones or 3rd generation cephalosporins and use of antibiotics for clinical signs that were recommended against antibiotic use by the guidelines.)~~

Underdosing was recorded in 131/486 (26.9%) cases. Cycling antibiotics occurred in 97/467 (i.e. 20.8%, 19 patients were prescribed two antibiotics from the start of their treatment), following apparent failure of a first antibiotic, cases were prescribed a second antibiotic without supportive culture and sensitivity results.). There were 91/486 (18.7%) cases that were prescribed a fluoroquinolone or third generation cephalosporin, and ~~I~~inappropriate prescription of these two classes of antibiotics occurred ~~There were 91/486 (18.7%) cases that were prescribed a fluoroquinolone or third generation cephalosporin,~~ in~~of which~~ 81/91 (89.0%) cases. ~~were prescribed when another more appropriate class could have been prescribed.~~ A culture and sensitivity test had been performed in 1/91 cases that were prescribed these class of antibiotics.~~.~~

Following apparent failure of a first-line antibiotic, 97/486 (19.9%) cases were prescribed a second line antibiotic without supportive culture and sensitivity results. Underdosing was recorded in 131/486 (26.9%) cases.

There were 232/486 (47.7%) cases that had been prescribed antibiotics for clinical signs where antibiotics are not recommended by the Protect/ProtectME guidelines.

Of the patients who received a prior antibiotics as indicated by UK guidelines, only clinical variables met SIRS/sepsis criteria, 13/20 dogs and 3/7 cats who met these criteria subsequently received antibiotics which did not adhere to UK guidelines (Supporting information S3, S4 and S5).

One hundred and eleven (47.8%) cases did not adhere with the guidelines in two different ways, 31 (17.7%) cases in three different ways and 8 (3.4%) cases in the four ways (i.e. underdosing, cycling antibiotics, inappropriate prescription of fluoroquinolones or 3rd generation cephalosporins and use of antibiotics for clinical signs that were recommended against antibiotic use by the guidelines.)

Bacterial infection documented

After investigations within a referral centre setting, a bacterial aetiology was found in 5566/486 (113.36%) cases that received antibiotics, and was suspected in a further 3251 (6.610.5%) cases. Therefore, a bacterial aetiology was found or suspected in 17.924.1% of the cases that received antibiotics. For one cat included here, *Helicobacter spp* was diagnosed within gastric biopsy samples.

DISCUSSION

Our data demonstrates that substantial improvement on adherence to antibiotic guidelines in general practice in the UK can be made as in 70.986% of the cases referred to internal medicine or oncology the guidelines were not followed. It also demonstrates over-prescription of antibiotics and infrequent use of appropriate tools ~~uncommon use of tools~~ to diagnose bacterial infection such as culture or cytology.

Three general approaches have been recommended to help limit antibiotic resistance: a) preventing disease occurrence, b) reducing overall antibiotic use and c) improved antibiotic use (Weese *et al.*, 2015).

Setting aside prevention of disease, which was not a focus of our study, and focusing on the approach of reducing overall antibiotic use, our data demonstrated an over-prescription of antibiotics in general practice in the UK relative to indication. This study reports that ~~in~~ 17.9~~24.1~~% of the cases who had received antibiotics and were referred to internal medicine and oncology services ultimately had a bacterial aetiology confirmed or suspected at the referral centre. In an attempt to limit an underestimation of cases with a bacterial aetiology, we included both confirmed and suspected bacterial aetiology as categories for analysis.

Various drivers have been attributed to the over-prescription of antibiotics in veterinary practice. This includes client factors such as perceived client satisfaction, commercial pressures to retain clients and the symbolic value of giving treatment (Smith *et al.*, 2018). Interestingly however, this was not borne out in pet owner surveys, where pet owners reported a perception of over-prescription by veterinarians (Smith *et al.*, 2018). Additional contributing factors to consider may include time pressures and clinical and financial resources available to allow a definitive diagnosis.

Focusing on the approach to limit AR of improved antibiotic use, the Protect / ProtectMe Guidelines attempt to guide veterinarians when antibiotics might be appropriate, and thereby reduce unnecessary prescription. Our data demonstrates poor adherence to antibiotic guidelines.. The most common way in which the Protect/ProtectMe guidelines were not followed was the prescription of antibiotics for clinical signs for which the guidelines were specifically advising veterinarians against, which happened in 47.7% of the cases that received antibiotics. Of those, the most common were uncomplicated vomiting and/or diarrhoea. In addition to breaking from the Protect / ProtectMe guidelines, this also goes against additional antibiotic use guidelines, where recommendations around managing enteropathogenic bacterial infections recommend reserving antibiotics for patients demonstrating signs of sepsis (Marks *et al.*, 2011). Furthermore, although a recent study suggests that metronidazole can shorten duration of acute non-specific diarrhoea in some dogs (Langlois, Koenigshof and Mani, 2020), multiple other veterinary studies indicate a limited benefit (Jergens *et al.*, 2010; Shmalberg *et al.*, 2019; Werner *et al.*, 2020, Busch *et al.*, 2015)). For chronic enteropathies, current ~~local~~ UK antibiotic guidelines consider appropriate a four-week trial of antibiotics for determining if the clinical presentation is antibiotic-responsive. However, a recent publication proposes antibiotic use is reserved until other therapeutic trials are proven unsuccessful, including diet/pre-probiotics or immunosuppressive drugs (Cerquetella *et al.*, 2020).

In our cohort, metronidazole was commonly prescribed to manage both acute and chronic gastrointestinal disorders, similar to data collected across Europe (Hughes *et al.*, 2012). Whilst metronidazole is a popular choice to manage *Clostridial sp.* in people, the role of *Clostridial sp*. in canine diarrhoea syndromes remains uncertain (Busch *et al.*, 2015). Metronidazole also disrupts the normal canine microbial flora, and is associated with an increased risk of becoming a carrier for multi-drug-resistant *Escherichia coli* (Gibson *et al.*, 2011; Igarashi *et al.*, 2014). Further, it may increase the risk of bacterial translocation, which has been shown in laboratory mice. (Wells *et al.*, 1987).

Another clinical sign in which antibiotics were frequently prescribed but which contradicted Protect/ProtectMe guidance against their use was feline lower urinary tract signs. Similar to recommendations within the ISCAID guidelines (Weese *et al.*, 2011, 2019), Protect/ProtectMe guidelines state that bacterial culture and susceptibility testing should be performed in all cases of suspected bacterial cystitis. However, an update to those guidelines (Weese *et al.*, 2019), was not available for use at the time of the study, with older guidelines (Weese *et al.*, 2011) conflicting with Protect / ProtectMe guidance in that they supported empiric antibiotic therapy while awaiting culture and susceptibility results to relieve patient discomfort. This could have been one reason why antibiotics were prescribed in this setting. Current recommendations are to confirm a diagnosis of bacterial cystitis, by culture, in all feline patients due to the low likelihood of bacterial cystitis in cats. Further to this, clinical signs of bacterial cystitis are frequently a result of inflammation and there is some evidence from humans that analgesics alone may be as effective as antibiotics in uncomplicated cases (Bleidorn *et al.*, 2016).

Both polyuria/polydipsia and canine sino-nasal disease were also associated with poor adherence to Protect / ProtectMe guidelines. Multiple aetiologies can result in polyuria and polydipsia in dogs and cats, with antibiotics only necessary where a septic focus is identified or strongly suspected. Primary bacterial rhinitis is an uncommon entity in dogs, with bacterial rhinitis more likely to occur as a sequela to inhaled foreign bodies or as a consequence of loss of turbinates resulting from mycotic disease, or trauma. In these cases, antibiotics might improve clinical signs but rarely permanently (Windsor *et al.*, 2006) ~~(Windsor and Johnson, 2006)~~.

In human medicine sepsis guidelines, antibiotics are recommended within one hour of recognition in patients with septic shock or high likelihood/confirmed of sepsis, given the strong association of antibiotic timing and mortality (Evans *et al.*, 2021). SIRS/sepsis criteria were assessed as a possible reason why antibiotics may have been prescribed in these patients in which assessing clinical signs alone, the prescription was considered inappropriate. Only 6.9% of the population met the criteria for SIRS/sepsis at the time they were prescribed with antibiotics. However, only 85 (21.8%) dogs and 9 (9.4%) cats had criteria available at the time of antibiotic prescription to make some assessment for SIRS, with the vast majority not having complete criteria available. Of those, 36.2% of the animals met the SIRS criteria, although a significant proportion of these were classified based upon 2 or 3 criteria alone. It is difficult to make robust conclusions around the incidence of SIRS in this cohort given the vast majority of cases prescribed antibiotics had insufficient information available to make an assessment at all. This could reflect those parameters were normal but were not documented, were not assessed due to short consultation durations in general practise in the UK, or a lack of emphasis regarding the importance of those factors in decision making around antibiotic use.

Failure to confirm a bacterial aetiology and evaluate antibiotic susceptibilities leads to the misuse of antibiotics, and does not allow veterinarians to make adequate choices around appropriate prescription (EMA, 2015; The Veterinary Medicines, 2015; Weese *et al.*, 2015). The data from our study demonstrates that antibiotic prescription was based on results of culture and sensitivity in only 8.8% of cases, whilst cytology was used in only 1.8% of cases, with only a very small number of cases having both. This is similar to data reported elsewhere, where only approximately half of veterinarians surveyed considered bacterial culture and sensitivity as important prior to prescribing antibiotics with fewer (30%) considering cytology useful (Hughes *et al.*, 2012).

Prescription of beta-lactams was common in our study, similar to previous publications from the UK (Mateus *et al.*, 2011; Radford *et al.*, 2011). The most common prescribed beta-lactam were penicillins, which were prescribed in 71.5% of dogs and 49.0% of cats. Nitroimidazoles (i.e. metronidazole) was the second most commonly prescribed antibiotic class in dogs, higher than in other reports (Mateus *et al.*, 2011; Radford *et al.*, 2011). This difference could be attributed to a population bias of patients referred to Internal Medicine, where gastrointestinal signs may be more common than within the general population and metronidazole is commonly prescribed in cases with diarrhoea as previously mentioned

(Hughes *et al.*, 2012). In cats, third generation cephalosporins were the second most used antibiotic, more specifically cefovecin. This antibiotic choice was significantly different between cats and dogs. This has previously been reported in the UK and Europe after authorisation of cefovecin, and likely reflects ease-of-use of long-acting injections in a species frequently non-compliant with oral therapeutics (~~Curt-, Simon and Huckabee~~Levy, 1998; Mateus *et al.*, 2011; Burke *et al.*, 2017). Cost associated with cefovecin administration may also negatively impacts use in dogs (Mateus *et al.*, 2011).

Fluoroquinolones or third generation cephalosporins were inappropriately prescribed in 89.0% of the cases receiving these classes of antibiotics, as culture and sensitivity had not been performed, and/or as other agents could have been used (Collignon *et al.*, 2016). The WHO classifies these antibiotic classes as highest priority critically important antibiotics and it has even been suggested that use of these antibiotics should be banned in animals to preserve their effectiveness in human medicine (Hughes *et al.*, 2012; Collignon *et al.*, 2016). However, there are concerns that a complete ban in veterinary medicine could be detrimental to animal health and welfare (Hughes *et al.*, 2012). ~~Local~~ UK antibiotic guidelines recommend use only when an antibiotic better aligned with prescribing guidelines is inappropriate and/or ineffective, and culture/sensitivity testing indicates that they will be effective.

Underdosing of antibiotics was documented in 26.9% of the cases included in our study, and this practice could result in subinhibitory concentrations and resistance (Choe *et al.*, 2000; Gillespie *et al.*, 2005; Ungemach, Müller-Bahrdt and Abraham, 2006). Reasons for underdosing were not always apparent. Miscalculations or rounding dosages to the nearest tablet size are considered possibilities.

Our study has several limitations that reflect its retrospective nature, a referral population bias, and within that, limitation to Oncology and Internal Medicine disciplines. As is frequently the case with retrospective studies, data was not always complete regarding clinical signs, antibiotic prescription, and physical examination. We included cases where a bacterial aetiology was "suspected" as one of the differential diagnosis based upon comment in the referral communications, but it is possible that differentials associated with suspected bacterial infection were not mentioned.

On its own, a referral population could be expected to bias data through increased case complexity and perhaps a higher frequency of antibiotic use. Further restriction to only Internal Medicine and Oncology cases could theoretically be expected to increase the overall antibiotic prescription frequency in this cohort, compared to ~~where~~ other disciplines if they were ~~are~~ also included. Discipline restriction could also have impacted choices around antibiotic classes prescribed, for example exclusion of Dermatology might be expected to comparatively reduce prescription of cephalosporins.

We decided to investigate ~~this~~ a referral population as they underwent extensive referral investigations so we considered that that appropriateness of the use of antibiotics could be addressed better than in cases without it. However, our findings may under-represent antibiotic prescriptions in a general practice setting, as cases that improved as a result of, or spontaneously irrespective of antibiotic prescription, are unlikely to be referred.

Lastly, between the two referral hospitals included, different timeframes were assessed, however this is considered unlikely to cause a significant shift in prescription patterns. This timeframe did cover an update on the guidelines in November 2018, however we limited the recommendations assessed and included to those present in both versions.

Specific ~~local~~UK guidelines were assessed, and it is possible that veterinarians were following a different antibiotic guideline with conflicting recommendations. Apart from the discussed previously regarding feline lower urinary tract disease and chronic diarrhoea already mentioned, no other conflicting recommendations were found.

Given roles in managing domestic animals with close human bonds, as well as roles within the human food chain, veterinarians have an integral role in promoting responsible use of antibiotics. It has been estimated that without proactive solutions to slow rising antibiotic resistance, or discovery of new antibiotics, that 10 million lives a year will be at risk by 2050 (Neill, 2014) We were not able, and did not set out, to evaluate veterinarians knowledge or understanding of existing antibiotic stewardship guidelines, or to determine what barriers might lead to non-compliance. However, our data identifies several aspects worthy of further exploration and investment in improving education around appropriate diagnostics, antibiotic class and dosage choices, thereby leading to improved compliance within antibiotic stewardship guidelines and more responsible use of antibiotics.

In conclusion, over prescription of antibiotics, poor adherence to ~~local~~ UK antibiotic guidelines and infrequent use of diagnostics such as culture and cytology to guide antibiotic use was observed.

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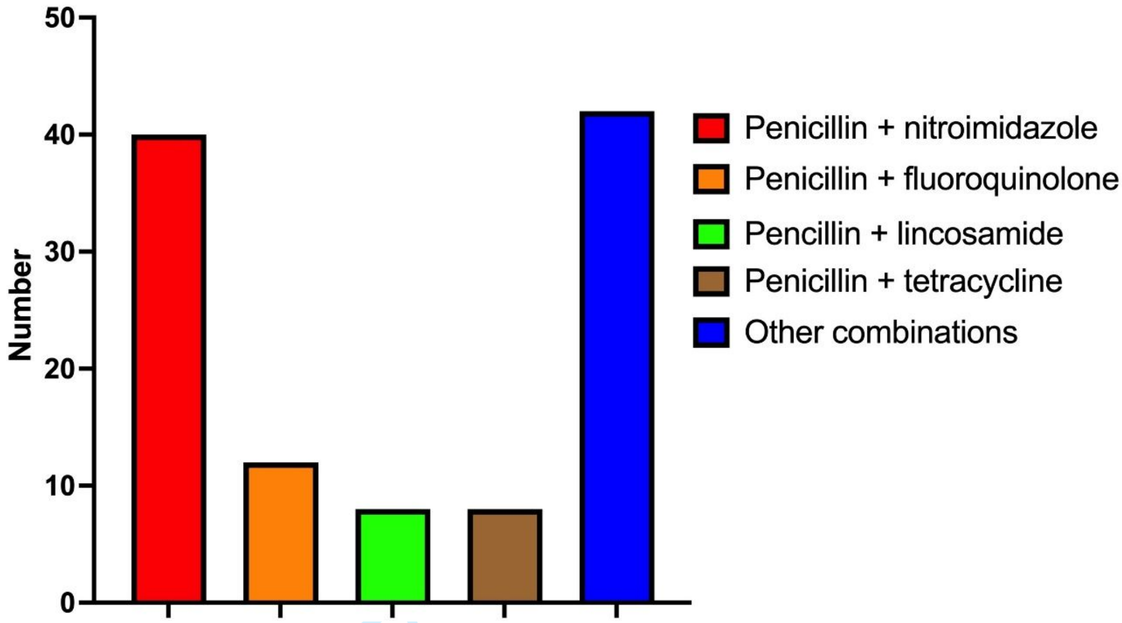

Figure 1. Most common combinations of antibiotic classes in dogs

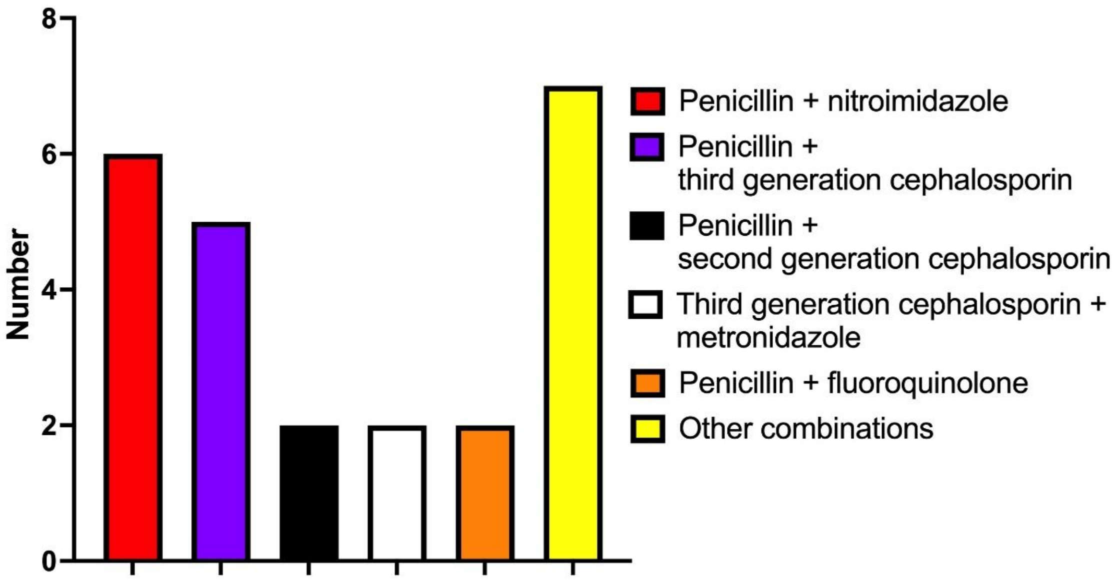

Figure 2. Most common combinations of antibiotic classes in cats

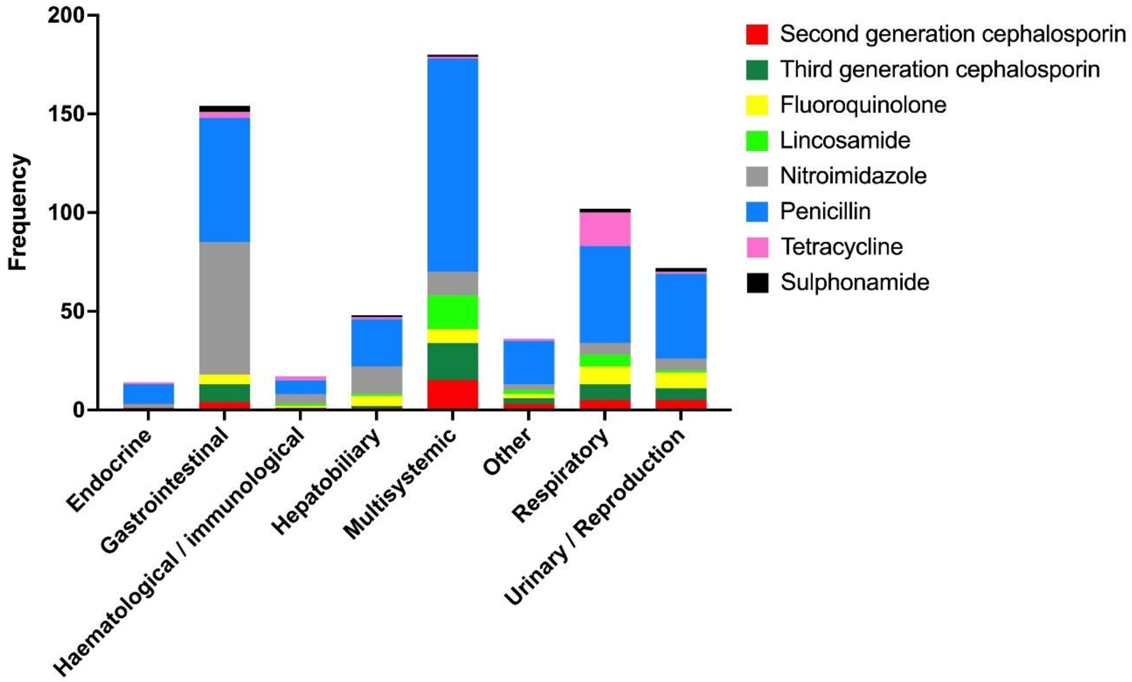

Figure 3. Antibiotic classes prescribed for each body system.

Antibiotic type	Number of dogs (%)	Number of cats (%)
Penicillins (ampicillin, amoxicillin, amoxicillin-clavulanate)	280 (71.8%)	49 (50.5%)
Nitroimidazoles (metronidazole)	102 (26.2%)	14 (14.4%)
Fluoroquinolones (enrofloxacin, marbofloxacin, pradofloxacin)	31 (7.9%)	11 (11.3%)
Tetracyclines (doxycycline, oxytetracycline)	22 (5.6%)	6 (6.2%)
Lincosamides (lyncomicin, clindamycin)	25 (6.4%)	4 (4.1%)
Cephalosporines 1st and 2nd generation (cefuroxime, cephalexin)	31 (7.9%)	6 (6.2%)
Cephalosporines 3rd generation (cefovecin)	15 (3.8%)	34 (35.1%)
Sulfonamides (trimetoprin-sulfonamide, sulphasalazine)	9 (2.3%)	0 (0%)
Aminoglycosides (amikacin)	0(0%)	1 (1%)
Macrolides (erythromycin)	1 (0.25%)	0 (0%)

Table 1. Types of antibiotics prescribed prior to referral in dogs and cats.

Supporting information S1 (patients characteristics)

Institute	Discpline	Species		Gender and neutered status	Frequency (n)	Percent
A	medicine	dog		male neutered	89	42,2
				male entire	28	13,3
				female neutered	74	35,1
				female entire	19	9
				Total	210	99,5
			Missing		1	0,5
			Total		211	100
		cat		male neutered	32	59,3
				female neutered	20	37
				female entire	2	3,7
			Total		54	100
B	medicine	dog		male neutered	129	41,5
				male entire	46	14,8
				female neutered	104	33,4
				female entire	32	10,3
			Total		311	100
		cat		male neutered	40	44,4
				male entire	7	7,8
				female neutered	40	44,4
				female entire	3	3,3
			Total		90	100
	oncology	dog		male neutered	89	41
				male entire	24	11,1
				female neutered	83	38,2
				female entire	14	6,5
				Total	210	96,8
			Missing		7	3,2
			Total		217	100
		cat		male neutered	17	50
				female neutered	14	41,2
				Total	31	91,2
			Missing		3	8,8
			Total		34	100

Supporting information S2 (treatment with antibiotics prior to referral)

Institute	Discpline	Treated with antibiotics prior to referral	Body system	Frequency (n)	Percent
A	medicine	yes	endocrine	4	3
			gastrointestinal	41	30,4
			haematological/ immunological	11	8,1
			hepatobiliary	16	11,9
			multi-systemic	5	3,7
			other	11	8,1
			respiratory	22	16,3
			urinary / reproduction	25	18,5
			Total	135	100
		no	endocrine	7	5,4
			gastrointestinal	23	17,7
			haematological/ immunological	12	9,2
			hepatobiliary	6	4,6
			multi-systemic	29	22,3
			other	26	20
			respiratory	12	9,2
			urinary / reproduction	15	11,5
			Total	130	100
B	medicine	yes	endocrine	9	4,2
			gastrointestinal	61	28,2
			haematological/ immunological	2	0,9
			hepatobiliary	19	8,8
			multi-systemic	23	10,6
			other	18	8,3
			respiratory	54	25
			urinary / reproduction	30	13,9
			Total	216	100
		no	endocrine	26	14,1
			gastrointestinal	44	23,8
			haematological/ immunological	5	2,7
			hepatobiliary	27	14,6
			multi-systemic	19	10,3
			other	29	15,7
			respiratory	20	10,8
			urinary / reproduction	15	8,1
			Total	185	100
	oncology	yes	gastrointestinal	1	0,7
			haematological/ immunological	1	0,7
			hepatobiliary	1	0,7
			multi-systemic	128	94,8
			other	3	2,2
			urinary / reproduction	1	0,7
			Total	135	100
		xf	oncology	116	100

Supporting information S3 (antibiotic compliance)

institute	discpline	body system	local antibiotic guidelines followed?	1st and 2nd generation cephalosporin (n)	3rd generation cephalosporin (n)	fluoroquinolone (n)	lincosamide (n)	nitrimidazole (n)	pencillin (n)	tetracycline (n)	sulphonamide (n)
A	medicine	endocrine	yes	1	1	1	1	1	1	1	1
			no	3	3	3	3	3	3	3	3
		gastrointestinal	yes	2	2	2	2	2	2	2	2
			no	39	39	39	39	39	39	39	39
		haematological / immunological	yes	3	3	3	3	3	3	3	3
			no	8	8	8	8	8	8	8	8
		hepatobiliary	yes	2	2	2	2	2	2	2	2
			no	13	13	13	13	13	13	13	13
		multi-systemic	yes	1	1	1	1	1	1	1	1
			no	3	3	3	3	3	3	3	3
		other	yes	7	7	7	7	7	7	7	7
			no	2	2	2	2	2	2	2	2
		respiratory	yes	6	6	6	6	6	6	6	6
			no	16	16	16	16	16	16	16	16
		urinary / reproduction	yes	13	13	13	13	13	13	13	13
			no	11	11	11	11	11	11	11	11
B	medicine	endocrine	yes	2	2	2	2	2	2	2	2
			no	7	7	7	7	7	7	7	7
		gastrointestinal	yes	8	8	8	8	8	8	8	8
			no	53	53	53	53	53	53	53	53
		haematological / immunological	yes	1	1	1	1	1	1	1	1
			no	1	1	1	1	1	1	1	1
		hepatobiliary	yes	6	6	6	6	6	6	6	6
			no	13	13	13	13	13	13	13	13
		multi-systemic	yes	7	7	7	7	7	7	7	7
			no	17	17	17	17	17	17	17	17
		other	yes	5	5	5	5	5	5	5	5
			no	13	13	13	13	13	13	13	13
		respiratory	yes	13	13	13	13	13	13	13	13
			no	41	41	41	41	41	41	41	41
		urinary / reproduction	yes	16	16	16	16	16	16	16	16
			no	14	14	14	14	14	14	14	14
	oncology	gastrointestinal	yes	1	1	1	1	1	1	1	1
			no	1	1	1	1	1	1	1	1
		haematological / immunological	no	1	1	1	1	1	1	1	1
		multi-systemic	yes	43	43	43	43	43	43	43	43
			no	85	85	85	85	85	85	85	85
		other	yes	1	1	1	1	1	1	1	1
			no	2	2	2	2	2	2	2	2
		urinary / reproduction	no	1	1	1	1	1	1	1	1

Supporting information S4 (reason for no compliance)

Chi-squared significance value								
	Antibiotic							
	1st and 2nd generation cephalosporin	3rd generation cephalosporin	fluoroquinolone	lincosamide	nitrimadazole	penicillin	tetracycline	sulphonamide
underdosed	0,565	0,061	0.029*	0,638	0.009*	0,435	0,137	0,142
used as second line with no bacterial culture	0.019*	0,568	<0.001*	0,116	<0.001*	0.001*	<0.001*	0,272
used as inappropriate prophylaxis	0,257	<0.001*	<0.001*	0,48	0.003*	<0.001*	0,977	0,373
used for condition where the antibiotic is not indicated	0,171	<0.001*	0.016*	0,256	0.006*	0.031*	0.012*	0,428

Supporting information S5 (Adherence to local guidelines)

			Adherence to local guidelines	
			yes	no
Body system	**endocrine**	Count	3	10
		Expected Count	3,7	9,2
		% within Body_system	23,10%	76,90%
		Adjusted Residual	-0,4	0,5
	gastrointestinal	Count	11	92
		Expected Count	29,3	73,1
		% within Body_system	10,70%	89,30%
		Adjusted Residual	-4,5	4,6
	haematological / immunological	Count	4	10
		Expected Count	4	9,9
		% within Body_system	28,60%	71,40%
		Adjusted Residual	0	0
	hepatobiliary	Count	8	27
		Expected Count	10,2	25,5
		% within Body_system	22,20%	75,00%
		Adjusted Residual	-0,9	0,6
	oncology	Count	51	105
		Expected Count	44,7	111,4
		% within Body_system	32,50%	66,90%
		Adjusted Residual	1,4	-1,4
	other	Count	13	17
		Expected Count	8,5	21,3
		% within Body_system	43,30%	56,70%
		Adjusted Residual	1,9	-1,8
	respiratory	Count	19	57
		Expected Count	21,6	53,9
		% within Body_system	25,00%	75,00%
		Adjusted Residual	-0,7	0,9
	urinary / reproductive	Count	29	26
		Expected Count	15,9	39,7
		% within Body_system	51,80%	46,40%
		Adjusted Residual	4,1	-4,3