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Usage patterns of carbapenem antimicrobials in dogs and cats at a veterinary tertiary care hospital

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Abstract

Background: Carbapenems are a class of antimicrobials reserved for resistant infections or systemically ill people, yet the extent and context in which they are prescribed in the small animals is understudied.

Hypothesis/Objective: To describe cases in dogs and cats treated with carbapenems to establish baseline data regarding the types of infections, outcomes, and resistance profiles of target infections. We hypothesize that prescribing practices for carbapenems at a veterinary tertiary care hospital would not comply with the recommended use guidelines in human medicine.

Methods: Retrospective study of veterinary medical records from all dogs and cats prescribed carbapenems between May 1, 2016, and April 30, 2017.

Results: A total of 81 infections (71 in dogs and 10 in cats) representing 68 animals (58 dogs and 10 cats) involving carbapenem use were identified. Cultures were performed in 65/81 (80%) infections, and antimicrobial use was de-escalated or discontinued in 10/81 (12%) infections. The average duration of treatment was 27.5 days and ranged from 1 to 196 days. Resistance to more than 3 antimicrobial classes was present in 57/115 (50%) isolates. Resistance to carbapenems was found in 2/64 (3%) of the bacterial isolates with reported carbapenem susceptibility.

Conclusions and Clinical Importance: The majority of carbapenem use at a veterinary tertiary care hospital was prescribed in conjunction with culture and sensitivity determination, with de-escalation performed in a minority of cases, and treatment durations longer than typically recommended in human medicine.

KEYWORDS
antimicrobial resistance, antimicrobial stewardship, guidelines, imipenem, meropenem

1 | INTRODUCTION

The World Health Organization (WHO) categorizes antimicrobials into 3 separate categories: critically important, highly important, and

important. There are 2 criteria that must be met for the "critically important" categorization: (1) the antimicrobial class is the sole available treatment for a serious bacterial infection and (2) the antimicrobial class is used to treat infections in people caused by bacteria

transmitted from nonhuman sources, or bacteria that can acquire resistance genes from nonhuman sources. Carbapenems meet both of these criteria and are therefore classified as "critically important" antimicrobials in human medicine.[1]

Carbapenems have a broad spectrum of activity against gram-positive and gram-negative aerobes and anaerobes. They are used to treat multidrug resistant (MDR) *Enterobacteriaceae* infections, including *Escherichia coli* and *Salmonella*,[1] and their effectiveness in treating resistant organisms is largely because of their resistance to destruction by beta-lactamases.[2] Because of their importance in treating life-threatening infections in human and veterinary medicine, judicious use of carbapenems is recommended, and there are multiple sets of guidelines for appropriate use in humans.[3-6]

In human medicine, imipenem-cilastatin is used primarily for hospital-acquired and healthcare-associated pneumonia, intra-abdominal infections, neutropenic fever, complicated urinary tract infections (UTIs), polymicrobial necrotizing fasciitis, severe diabetic foot infections, and osteomyelitis.[7] Meropenem is primarily used for skin and soft tissue infections, intra-abdominal infections, acute pancreatitis, obstetric and gynecologic infections, respiratory infections, bacterial meningitis, and febrile neutropenia.[8] Many of the human clinical conditions for which these drugs are used are characterized by high rates of drug resistance or by complicated mixed infections.[3]

Meropenem's first reported use in veterinary medicine was in Brazil in 1999 as a treatment for conjunctivitis.[9] Its spectrum is similar to imipenem, but meropenem is more active against *Enterobacteriaceae* and less active against gram-positive bacteria. Although not approved for veterinary use, both are prescribed legally in some jurisdictions for extralabel use, primarily for the treatment of resistant infections in dogs and cats, and especially MDR *E. coli* isolates.[8,9] There are currently scant data on prescribing patterns and little guidance regarding appropriate use of carbapenems in small animal veterinary medicine.

The goal of this retrospective study was to review cases over the course of 1 year at a veterinary tertiary care hospital in which either imipenem or meropenem was prescribed to cats and dogs, to determine the type of infection they were used to treat and whether the infection was cultured before prescribing a carbapenem, duration of treatment, if antimicrobial treatment was de-escalated with culture results, and survival statistics for dogs and cats in which carbapenems were used. Understanding current prescribing patterns is a first step in providing guidance for and targeting stewardship interventions.

2 | MATERIALS AND METHODS

2.1 | Study design and overview

This is a retrospective study of medical records of dogs and cats over a 1-year period (May 1, 2016, to April 30, 2017) at a veterinary tertiary care hospital. The electronic medical record was searched for all cases that were prescribed meropenem or imipenem, and these data were collected: (1) species (dog or cat), (2) reason for hospitalization, (3) infection type(s), (4) whether the infection was hospital acquired, (5) culture sites, (6) culture and sensitivity results, (7) whether or not

treatment was adjusted based on culture results, (8) duration of treatment, and (9) outcome defined as survival to discharge and survival to 1 month after first instance of carbapenem use.

2.2 | Data analysis

Stata/IC14.0 was used for statistical analysis. Normality was evaluated graphically using histograms. Wilcoxon rank-sum tests were used to compare continuous variables between 2 groups. Kruskal-Wallis equality of populations rank tests were used to compare continuous variables between greater than 2 groups. Fisher's exact tests were used to compare categorical results between groups. *P* values <.05 were considered statistically significant.

2.3 | Study definitions

When reviewing the data, some dogs and cats had multiple instances of infection. The word "infection" refers to each instance in which a dog or cat presented to the hospital and underwent carbapenem treatment. Although most dogs and cats only presented once in the study period, some dogs and cats underwent multiple rounds of carbapenem treatment because of recurring or new infections. Each instance of carbapenem treatment dating 30 days or more from the end of the previous treatment course was considered a new infection. For coinfections, each bacteria cultured was called a "bacterial isolate." If an animal had multiple samples of the same infection cultured within 30 days, all cultures from that location were considered part of a single "infection."

Infection type was the infection targeted by carbapenem as determined by the written record. It differs from sites cultured as not every infection was cultured. Therefore, the variable infection type includes uncultured infections as well as cultured ones. In addition, infection types are different than the reason for being hospitalized in some instances as the infection type treated with carbapenems includes hospital-acquired infections (HAIs).

Hospital-acquired infections include central venous line-associated bloodstream infections, catheter-associated UTIs, surgical site infections, ventilator-associated pneumonia, and aspiration pneumonia associated with an anesthetic event.[10] All infections designated as HAI were identified at least 24 hours after hospitalization began or occurred within 7 days of discharge from hospital or from a surgical or anesthetic event.

Duration of use was determined by adding the number of days a carbapenem was used in the hospital to the prescribed days of medication taken home with the client. Client communication notes were read to ensure there were no changes to at-home treatment.

Carbapenems were used to treat organisms with varying levels of drug resistance. Antimicrobial resistance (AMR) classifications for each bacterial isolate were adapted from Thungrat et al[11]: non-drug resistant (NDR)—no resistance to any tested antimicrobial classes; non-multidrug resistant (single-drug resistant [SDR])—resistance to 1 or 2 tested antimicrobial classes; MDR—resistance to 3 or more categories of tested antimicrobial classes; or extreme drug resistant

(XDR)—resistance to all except 2 or fewer tested antimicrobial classes. Intrinsic resistance of a microbial species to an antimicrobial, such as *Enterococcus* resistance to cephalosporins, was not considered as acquired resistance and was thus excluded from consideration in AMR classification. All antimicrobial classes tested are included in Appendix. An isolate was determined to have resistance to an antimicrobial if it had either intermediate or full resistance to the antimicrobial. The ability to de-escalate treatment for an infection was considered present if a positive culture was obtained and documented susceptibility existed to any antimicrobial other than a carbapenem. For infections with isolates of different levels of AMR, the maximum resistance category was used for comparative analyses.

3 | RESULTS

3.1 | Demographics

During the study period, carbapenems were used in 81 infections (71 from dogs and 10 from cats), which represent 68 animals (58 dogs and 10 cats). Over the same period, 7929 cases (6258 dogs and 1671 cats) were admitted to the hospital. Dogs and cats in which carbapenems were used represent 0.35% of the hospital's total inpatient caseload in the time frame analyzed and 0.18% of the hospital's total caseload in the time frame analyzed.

Dogs were distributed across 38 breeds/mixes. Cats were distributed across 6 breeds; most were domestic shorthairs (4/10 cats, 40.0%). Animal ages ranged from 0 to 19 years of age, with a median of 11 years. The median age of dogs was 10 years (range, 1-14), and the median age of cats was 13 years (range, 0-19). Three dogs were excluded from the age count because of an unknown birth date. Demographic data are included in Table 1.

3.2 | Reason for hospitalization

In dogs, the most common reasons for hospitalization included pneumonia (32/71, 45%), UTI/pyelonephritis (11/71, 16%), non-specific febrile illness (6/71, 8%), and septic abdomen (3/71, 4.2%). In cats, the most common reasons for hospitalization were UTI/pyelonephritis (5/10) and biliary obstruction (2/10). Other reasons included cholangiohepatitis, pneumonia, and urethral obstruction (each 1/10).

3.3 | Infection types

The most common infection type targeted by carbapenem use in dogs was respiratory (34/71, 48%), followed by urinary (19/71, 27%), soft tissue (5/71, 7%), blood/systemic (4/71, 6%), abdominal (4/71, 6%), and other (5/71, 7%). The most common infection type in cats was urinary (6/10) followed by abdominal (3/10) and respiratory (1/10). There was no significant association between sex and overall type of infection; however, females were significantly more likely to have UTIs than males in both cats and dogs ($P < .03$).

TABLE 1 Demographic information and case characteristics for 71 infections in dogs and 10 infections in cats prescribed carbapenems at a tertiary care hospital between May 1, 2016, and April 31, 2017. Age is presented as a median and range; all other variables are presented as the number of infections (n) followed by the percentage of total instances

	n or median	% or range
Dog		
Age (years)	10	1-14
Breed		
Labrador Retriever	9	15.5
German Shepherd	3	5.2
Great Dane	3	5.2
Collie	3	5.2
Beagle	2	3.4
English Bulldog	2	3.4
Golden Retriever	2	3.4
French Bulldog	2	3.4
Bichon Frise	2	3.4
Miniature Schnauzer	2	3.4
Other	28	48.3
Total	58	100
Sex		
Male	27	46.6
Female	31	53.4
Cat		
Age (years)	13	0–19
Breed		
Domestic short hair	4	40
Ragdoll	2	20
Other	4	40
Total	10	100
Sex		
Male	5	50
Female	5	50

3.4 | Hospital-acquired Infections

Twelve of 71 (17%) infections in dogs and no infections in cats were hospital acquired. Nine of the 12 (75%) HAIs were aspiration pneumonia and 3/12 (25%) were associated with surgical sites. Four (4/12, 33%) HAIs were classified as XDR, 2/12 (17%) were classified as MDR, and 1/12 (8%) was classified as SDR. No HAIs were classified as NDR. One (1/12, 8%) HAI returned from culture testing with no bacterial growth, whereas 4/12 (33%) did not have a culture submitted.

3.5 | Cultures performed

Cultures were performed in 65/81 (80%) infections. Of the 71 infections involving dogs, 55/71 (78%) were cultured. Of the 10 infections involving cats, all 10 were cultured (Figure 1). As some dogs and cats
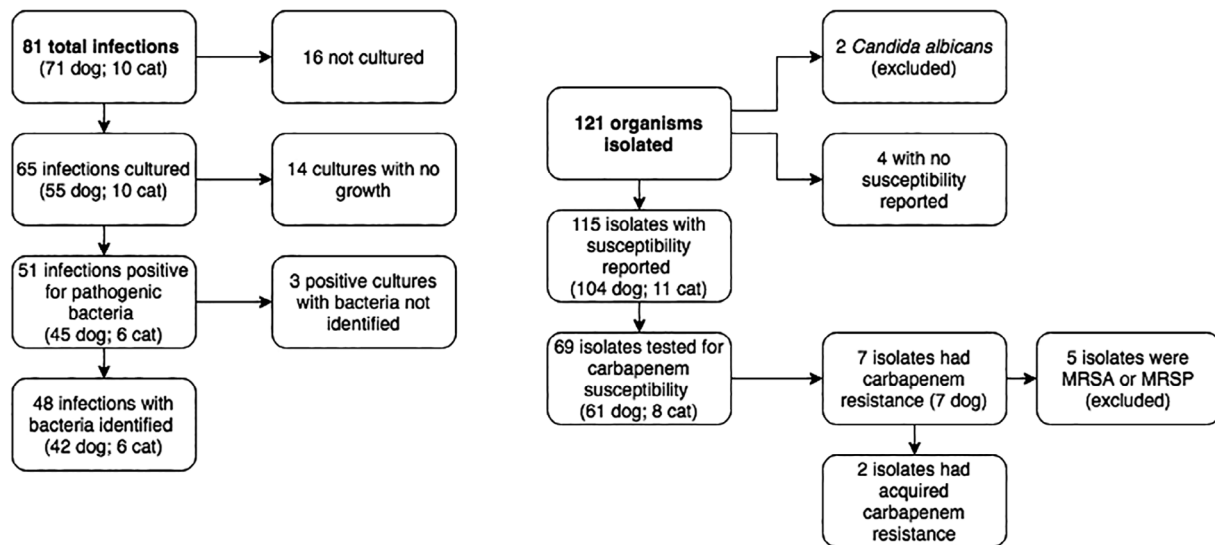
FIGURE 1 Flowchart displaying the process of exclusion of infections and isolates from analysis

TABLE 2 The most common microbial isolates from the 5 most common infection locations in dogs and cats. "Other" included infections in the ear and joints

Location	Number of isolates	Escherichia coli n (%)	Enterococcus n (%)	Staphylococcus n (%)	Klebsiella n (%)	Pseudomonas n (%)	Enterobacter n (%)
Urinary	49	19 (38.8)	20 (40.8)	3 (6.1)	3 (6.1)	2 (4.1)	0 (0.0)
Respiratory	27	9 (33.3)	2 (7.4)	4 (14.8)	4 (14.8)	2 (7.4)	1 (3.7)
Soft tissue	19	3 (15.8)	4 (21.1)	3 (15.8)	0 (0.0)	0 (0.0)	4 (21.1)
Abdominal	22	7 (31.8)	13 (59.1)	1 (4.5)	0 (0.0)	0 (0.0)	1 (4.5)
Other	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (75.0)	0 (0.0)

had multiple cultures performed, a total of 116 cultures, 101 in dogs and 15 in cats, were performed. In dogs, the most common culture sites included the urinary tract (43/101, 43%), respiratory tract (25/101, 25%), abdomen (including the peritoneum, liver, gall bladder, and pancreas; 15/101, 15%), cutaneous wounds or abscesses (7/101, 7%), and blood (6/101, 6%). Other culture sites included the ear, joint cavity, and the lumen of a jugular catheter (5/101, 5%). In cats, the culture sites were the urinary tract (10/15, 67%), abdomen (gall bladder or liver; 4/15, 27%), and respiratory tract (1/15, 7%).

3.6 | Culture and sensitivity results

Of the 65 cultured infections, 51 (79%) were positive for pathogenic bacteria, as defined by the reference laboratory (IDEXX Laboratories, Westbrook, Maine). Of the 51 positive cultures, 48 infections (94%) had specific bacteria identified (42 in dogs and 6 in cats), and 3 cultures were positive but not speciated. Twenty-five infections had 1 bacterial isolate (25/48, 52%), 17 had 2 isolates (17/48, 35%), 5 had 3 isolates (5/48, 10%), and 1 had 4 isolates (1/48, 2.1%). A total of 121 organisms were isolated, and 115/121 (95%) had their sensitivity determined. Two of 115 (1.7%) were identified as the yeast *Candida albicans* and were excluded from further analysis of carbapenem

susceptibility. Four additional isolates (4/115, 3.5%) were excluded from further analysis because the diagnostic laboratory did not determine susceptibility, stating that it was predictable (1 *Pasteurella* sp., 1 Beta-hemolytic *Streptococcus* sp., and 2 *Stenotrophomonas maltophilia*). The most common bacteria seen for each infection location and the proportion of each type of infection are shown in Table 2.

The most commonly isolated bacteria in dogs were *E. coli* (22/42, 52%), *Enterococcus* sp. (17/42, 41%), *Staphylococcus* sp. (11/42, 26%), *Klebsiella pneumoniae* (7/42, 17%), and *Pseudomonas aeruginosa* (n = 5/42, 12%). Six of the 11 *Staphylococcus* isolates were methicillin resistant (6/11, 55%). There were 2 bacteria cultured in cats: *E. coli* (5/6, 83%) and *Enterococcus* sp. (3/6). *Enterococcus* species was only identified in 1 case as *Enterococcus faecium*, which is intrinsically resistant to carbapenem antimicrobials.

Of the 115 bacterial isolates tested for susceptibility, 64 (56%) were tested for susceptibility to carbapenems (56 dogs and 8 cats), representing 37 infections (32 in dogs and 5 in cats). Methicillin-resistant *Staphylococcus* sp. was excluded from evaluation of carbapenem susceptibility as this designation implies resistance to all beta lactams. Two of 64 (3%) bacterial isolates demonstrated resistance to carbapenems, both from dogs. The resistant bacteria included *Pseudomonas* sp. (n = 1) and *Enterococcus* sp. (not speciated; n = 1).

Fifty-eight gram-negative isolates were tested for carbapenem resistance, and the only gram-negative isolate with carbapenem resistance was the isolate of *Pseudomonas* (1/58, 1.7%), which had intermediate resistance with an minimum inhibitory concentration (MIC) of 8 μg/mL. Carbapenems were utilized in infections of varying susceptibility to other antimicrobials, with most bacterial isolates displaying XDR (58/115, 50%); whereas some isolates were NDR (5/115, 4.3%; Table 3).

3.7 | Treatment change based on culture results

Forty-four of 81 (54%) infections were considered suitable for de-escalation of treatment based on susceptibility data. Eight culture-positive infections had treatment de-escalated from empirical carbapenem use (8/44, 18%), whereas treatment was discontinued in

TABLE 3　Resistance categories and distribution in each category among 115 bacterial isolates and 68 infections from dogs and cats prescribed a carbapenem at a tertiary care veterinary hospital between 2016 and 2017. Resistance was defined as no resistance to any tested antimicrobial classes (non-drug resistance [NDR]), non-multidrug, resistance to 1 or 2 tested antimicrobial classes (SDR), resistance to 3 or more categories of tested antimicrobial classes (MDR), or resistance to all except 2 or fewer tested antimicrobial classes (XDR)

AMR status	Bacterial isolates n (%)	Infections n (%)
XDR	58 (50.4)	29 (42.6)
MDR	34 (29.6)	22 (32.4)
SDR	18 (15.7)	14 (20.6)
NDR	5 (4.3)	3 (4.4)

Abbreviation: AMR, antimicrobial resistance.

1 infection after culture results returned (1/44, 2.3%). Of the 16 infections that initially had negative cultures (12 in dogs and 4 in cats), only 2 dogs had antimicrobial treatment de-escalated or discontinued (2/16, 13%). One culture-negative infection had treatment de-escalated empirically (1/16, 6%), whereas 1 culture-negative infection had treatment discontinued. Three culture-negative cases died before culture results returned that could have led to treatment de-escalation or discontinued treatment (3/16, 19%). There was no significant association between an indication to de-escalate based on culture and sensitivity results and whether de-escalation occurred ($P > .05$).

Of the 2 bacterial isolates with acquired carbapenem resistance, de-escalation to a lower-tier antimicrobial treatment regimen occurred in the case that had a positive culture for *Pseudomonas* sp. The *Pseudomonas* isolate was found in a nasal swab of a dog with a history of a complicated aspiration pneumonia in addition to an upper respiratory infection. A tracheal wash of the same dog during the same infection period yielded *E. coli*, beta-hemolytic *Streptococcus* sp., and *Staphylococcus simulans* in the same culture. An *Enterococcus* isolate was made from the second dog, which was resistant to all antimicrobials tested except vancomycin and linezolid. This isolate was from a bile duct swab of a complicated intra-abdominal infection that included *E. coli*, *Enterobacter cloacae*, *E. faecium*, and other *Enterococcus* species, isolated from different swabs of the abdomen. The dog was treated with vancomycin and the treatment was de-escalated to meropenem and was used after a later culture found a different isolate resistant to all tested antimicrobial classes except carbapenems.

3.8 | Duration of use

The duration of carbapenem treatment was not normally distributed, being heavily skewed to the right (Figure 2). The median number of days was 23, with a range of 1-196. Fourteen of 81 (17%) infections
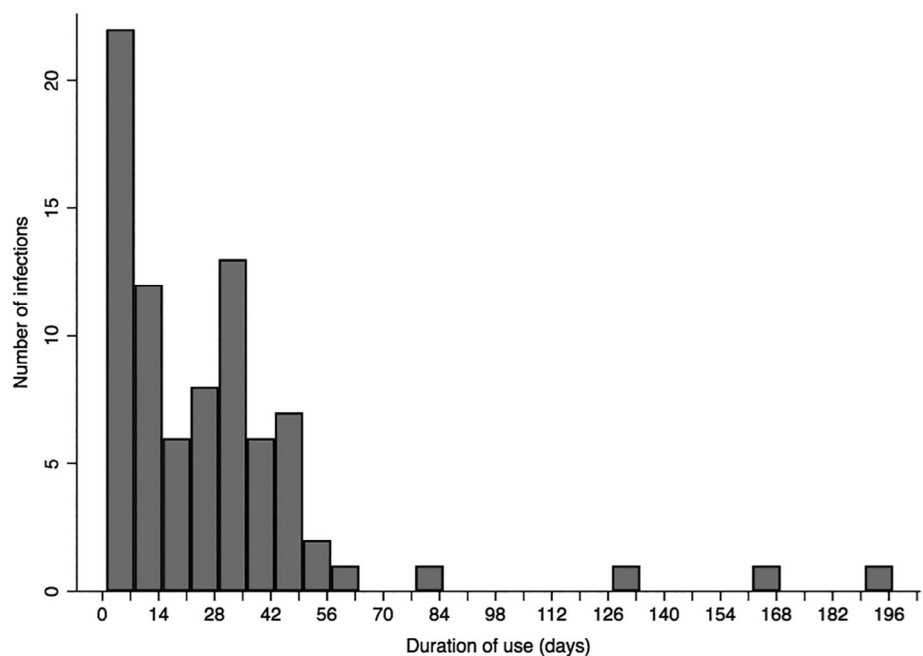

FIGURE 2　Histogram depicting durations of carbapenem use in 71 infections in dogs and 10 infections in cats from May 2016 to April 2017 (n = 81). Bin length is 7 days. Median duration was 23 days
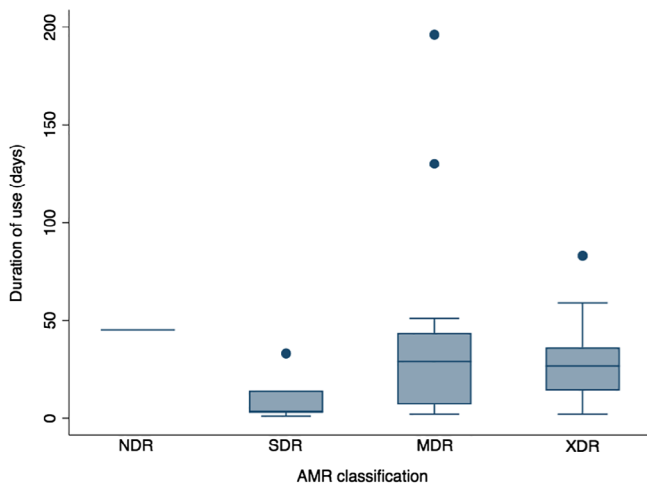
FIGURE 3 Box plot depicting durations of carbapenem use in 48 infections with known maximum antimicrobial resistance (AMR) classifications. Outliers included 33 (SDR), 130 (MDR), 196 (MDR), and 83 (XDR). MDR, multidrug resistant; SDR, single drug resistant; XDR, extreme drug resistant

were treated continuously for longer than 6 weeks. Twenty-three of 81 infections (28%) were treated for 10 days or less, and of these 14/23 (61%) died before the first 10 days of treatment were completed. There was no statistically significant difference in duration of use between dogs (mean, 26 days; median, 23 days; range, 1-162 days) and cats (mean, 37 days; median, 17 days; range, 3-196 days; $P = .94$), males (mean, 21 days; median, 22 days; range, 1-59 days) and females (mean, 32 days; median, 25 days; range, 1-196 days; $P = .29$), the 2 most common infection types (respiratory: mean, 27 days; median, 24 days; range, 1-162 days) and urinary: mean, 35 days; median, 25 days; range, 2-196 days; $P = .43$), or between HAIs (mean, 16 days; median, 8 days; range, 1-47 days) and non-HAIs (mean, 30 days; median, 24 days; range, 1-196 days; $P = .12$; Figure 3).

Sixty-three of 81 infections (78%) involved the continued administration of a carbapenem after hospital discharge and administered subcutaneously by the caregiver of the pet, including 55/71 (78%) infections in dogs and 8/10 in cats.

3.9 | Survival rates

Fifty-three of 68 animals (78%) survived until discharge. Forty-eight (48/68, 71%) survived to 1 month from their first instance of receiving a carbapenem (Table 2). In dogs, 45/58 (78%) survived until discharge and 41/58 (71%) survived over 1 month after first administration of carbapenems. In cats, 8/10 survived until discharge from the hospital and 7/10 survived a month after first administration of carbapenems.

4 | DISCUSSION

This retrospective study outlines the usage patterns of carbapenems, classified as critically important by the WHO, in dogs and cats at a veterinary tertiary care hospital over a 1-year period. In the past,

some veterinary hospitals have categorized carbapenems, along with vancomycin, as third-line antimicrobials, meaning they should only be used as drugs of last resort.[12] A survey of veterinary teaching hospital directors in the United States and Canada in the early 2000s found that only 3/21 who replied had any policy for the use of such drugs. Some did not use them, or used them rarely, whereas others commented they "do not like restrictions on their rights to prescribe".[13] Currently, there is scant data to show how this class of critically important drugs is being used in small animal veterinary medicine.

Multiple organizations recommend various guidelines for carbapenem use in veterinary medicine.[14-16] However, the guidelines vary in their scope, specificity, and type of infection. The International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for carbapenem use in UTIs state that the use of critically important antimicrobials in companion animals is only justified if (1) infection is documented based on clinical culture and cytological abnormalities, (2) resistance to all other reasonable options and susceptibility to the carbapenem chosen is documented, (3) the infection is potentially treatable (the animal will likely survive and the infection will likely be eventually cleared), and (4) consultation with an expert in infectious disease and antimicrobial treatment is sought.[16] For both imipenem and meropenem, guidelines from ISCAID for respiratory tract infections in companion animals state that they should be reserved "for the treatment of multidrug-resistant infections, particularly those caused by *Enterobacteriaceae* or *P. aeruginosa*...consultation with an infectious disease veterinary specialist or veterinary pharmacologist before use [is recommended]."[15] The British Small Animal Veterinary Association advises that there is a strong argument that carbapenems should not be used in small animal veterinary medicine at all.[17] Adherence to such guidelines is important because hospitals with stewardship programs have been shown to have significantly lower antimicrobial use compared to hospitals that do not implement interventions.[18]

This retrospective review of cases seen at a single tertiary veterinary small animal hospital over the course of 1 year begins to describe the usage patterns of this critically important drug class in dogs and cats. This hospital currently does not have any hospital-specific guidelines or policies restricting the use of carbapenems, so clinicians use the published guidelines described above to decide the best treatment for individual animals. Overall, the number of cases in which carbapenems are used as compared to the in-hospital population is quite low (<0.5%). Cultures were performed in over 80% of infections treated with carbapenems. This indicates general, although imperfect, compliance with guidelines recommending culturing an infection before carbapenem use. For the remaining non-cultured infections, there are many reasons a culture might not have been performed: owner refusal, financial constraints, patient risk (such as with a trans- or endo-tracheal washes for unstable pneumonia cases), or if the infection location could not be determined for sampling. The reasons are difficult to gather in a retrospective study, and a prospective study of a similar nature would allow for these data to be collected more thoroughly. Nonetheless, as dictated by the above guidelines, the use of carbapenems without documented infection and carbapenem susceptibility constitutes an area for improved antimicrobial stewardship.

When lower tier antimicrobials are used, empirical treatment is often acceptable. At 1 veterinary teaching hospital, the percent of infections for which a second-tier antimicrobial, enrofloxacin, was prescribed in which a culture was performed totaled 55%. For first-tier drugs, such as amoxicillin, cephalexin, or amoxicillin clavulanate, the percent of infections in which a culture was performed averaged only 14%.[19] Although this example only reflects the practices of 1 hospital, it allows us to compare the relative compliance to carbapenem guidelines that state that a bacterial culture must be performed before antimicrobial treatment is initiated. Overall, the percentage of infections treated with carbapenems that were cultured in this study is higher than what has been reported for first- and second-tier antimicrobial-treated infections, which might reflect clinician knowledge and awareness of recommended practices regarding carbapenem use. This might also be reflective of general clinician preferences for obtaining cultures at tertiary care hospitals compared to general practice clinics. Further insights into the prescribing practices and reasoning of clinicians in regard to carbapenems should be assessed through survey or other methods.

Finally, the data in this study show that dogs and cats treated with carbapenems had high survival rates (Table 4). According to the previously mentioned guidelines, carbapenems should be used in dogs and cats with a reasonable expectation of treatment success, and these data support reasonable patient selection practices.

Although no specific recommendations are available for duration of clinical use in veterinary medicine, recommendations for use in humans generally are for short courses, no longer than 7-10 days.[20,21] Recommendations for antimicrobial use of any kind in humans generally do not exceed 6 weeks.[22] In our study, treatment for only slightly more than 1 quarter of infections involved carbapenems used for 10 days or less, and many of those dogs or cats died before that number could be reached, likely indicating that treatment would have been longer than 10 days. Additionally, many infections were treated longer than the maximum recommendation in human medicine of 6 weeks of treatment. The longest duration of treatment was 196 days for a UTI, which was in a cat that had a history of previous carbapenem use.

Over 3 quarters of infections involved carbapenem use at home, meaning that many dogs and cats were prescribed this drug for long after the time of admission and discharge. In general, infections with isolates in higher AMR classes were treated for longer durations. Most of the infections with susceptibility results had a maximum AMR class of XDR (Table 3). Based on these data from a single tertiary care facility, the duration of use might be the area for biggest improvement in

stewardship. Additional, prospective, multi-institutional data to determine the duration of treatment for various diseases targeted by antimicrobials are needed in veterinary medicine.

Treatment was de-escalated for a small number of cases, despite the high percentage of cases in which treatment could have been de-escalated. We find it notable that culture results did not influence clinician prescribing, as clinicians were not more likely to de-escalate when the culture and sensitivity results demonstrated the ability to de-escalate. Perhaps factors other than susceptibility, such as severity of infection and response to treatment, are influencing clinicians' decisions to de-escalate or not, and indicates an area for potential stewardship intervention. These data also suggest that adoption of mechanisms to ensure clinicians reconsider antibiotic treatment and the potential for de-escalation every 2-3 days for hospitalized pets might be beneficial in improving stewardship efforts. Documented reasons not to de-escalate varied depending on the susceptibility to other drugs, renal health, and risks of keratoconjunctivitis sicca. Aminoglycosides, commonly the only other class to which a bacterial isolate had susceptibility among the analyzed cases, are often avoided because of their potential for nephrotoxicity, and thus require intensive monitoring and limited treatment duration.[23] Other infection treatments might not have been de-escalated because of the concern that not all organisms might have been successfully cultured. Over 50% of infections in this study had bacteria that were susceptible to 3 or more classes of antimicrobials, indicating another area where stewardship interventions could be targeted.

A total of 15% of infections treated with carbapenems were hospital acquired. Although some HAIs are unavoidable, all HAIs in this study involved resistant organisms, and thus reducing HAIs can decrease the need for carbapenem use. Infection control involving strict hand hygiene, appropriate surface disinfection, and a consistently clean surgical suite can all help reduce the number of nosocomial infections in a hospital.[24] To lower the risk for aspiration pneumonia, dogs and cats can be fasted preoperatively and particularly at-risk cases can have their esophagus and stomach suctioned before extubation.[25]

Overall, 2/64 (3.1%) bacterial isolates with sensitivity panels available from a culture showed resistance to carbapenems. Encouragingly, no cases of carbapenem-resistant *Enterobacteriaceae*, pathogens of concern in HAIs for humans, were found in the scope of this study. For the *Enterococcus* and *Pseudomonas* infections where carbapenem resistance was documented, treatment was de-escalated, or carbapenems were only used when resistance was present to all other antimicrobials. Similar to previous studies, *Enterococcus* sp. in our study often displayed high levels of resistance and were frequently cultured in combination with other organisms. Infection can resolve when treatment is aimed at the other bacteria present (most commonly Gram-negative and anaerobic organisms) rather than the resistant *Enterococcus*,[23] but in this study we were unable to identify consistent prescriber responses to *Enterococcus* coinfections. Polymicrobial infections represent another opportunity for prescriber education and potential de-escalation of treatment. Overall, during courses of carbapenem treatment, when carbapenem resistance was

TABLE 4 Survival statistics for animals with 81 infections involving carbapenem use at a tertiary care veterinary hospital from May 1, 2016, to April 30, 2017. Survival statistics for dogs and cats 1 month after first dose of carbapenem and to discharge from the hospital are reported. Seventy-one infections in dogs and 10 infections in cats were assessed

Outcome	Dog n (%)	Cat n (%)	Total n (%)
Survival to discharge	58 (82)	8 (80)	66 (82)
Survival to 1 month	54 (76)	7 (70)	61 (75)

1684 | Journal of Veterinary Internal Medicine

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SMITH ET AL.

present, the treatment was adjusted appropriately within the clinician's ability.

Limitations of this study included its small sample size and retrospective nature. Exact reasons for drug prescribing and lack of de-escalation were not always apparent from medical record review. Additionally, because of the retrospective nature of the study and lack of overall tracking systems for antimicrobial use in our hospital, it is not possible to say what proportion of dogs and cats hospitalized in the same time period received antimicrobial treatment. Furthermore, some dogs and cats presenting with chronic infections were counted multiple times for a new infection because of the 30-day mark of counting new infections, but it could have been a recurrence of the previous infection. This was not always clear from the data available. Being a tertiary care facility, cases seen might not be representative of other types of facilities, and might be more likely to include dogs and cats with MDR infections. Finally, resistance might be influenced by local prescribing practices or other regional factors, and not reflective of the level of resistance found in all locations. A prospective multi-institutional study is needed, and a survey of prescribing practices distributed to veterinarians would help clarify further describe prescribing patterns among clinicians that utilize carbapenems.

4.1 | Conclusions

This retrospective study of the usage patterns of carbapenems in dogs and cats at a tertiary small animal veterinary hospital showed that clinicians at our hospital are compliant with the recommendations by ISCAID to obtain cultures before carbapenem use and to use these drugs in dogs and cats with a high likelihood of survival. There is room for improvement in reduction of HAIs, duration of treatment, and actively de-escalating treatment regimens that have options other than carbapenems available. Implementation of hospital-level guidelines is effective in reducing the number of antimicrobial prescriptions without influencing patient outcomes. This could be particularly useful in reducing the duration of use of carbapenems in both humans and animals, which might help curb the development of resistance to this crucial drug class.[27-32]

Although there are gaps in our knowledge of the degree to which veterinary prescribing practices influence AMR in humans, the importance of maintaining the effectiveness of carbapenems for life-threatening human and veterinary infections cannot be denied, and there is evidence to support that carbapenem-resistant bacteria could be easily transferred from animals to humans.[13,33] This study identifies targets for future research and stewardship interventions for carbapenems in small animal veterinary medicine.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Antimicrobials described in this study are used off-label.

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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.