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Parenterally administered vancomycin in 29 dogs and 7 cats (2003-2017)

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Background: Vancomycin is commonly used to treat resistant bacterial infections in people. Reported adverse effects of vancomycin in people include acute kidney injury (AKI), neutropenia, and systemic allergic reaction. Given the increased incidence of vancomycin-resistant bacterial infections in people, support is growing for restriction of vancomycin.

Objectives: To evaluate the use of intravenous (IV) vancomycin in a university teaching hospital and to describe potential adverse effects.

Animals: Twenty-nine dogs and 7 cats.

Methods: Medical records of dogs and cats treated with IV vancomycin at the Foster Hospital for Small Animals between January 2003 and October 2017 were reviewed. Information recorded included signalment, infection source, vancomycin dosing, potential adverse effects, and outcome.

Results: Vancomycin was used to treat infections from a range of sources with a variety of dosing intervals. The most common bacterial isolates susceptible to vancomycin included *Enterococcus* sp. (11/36, 30.6%), methicillin-resistant *Staphylococcus aureus* (8/36, 22.2%), and methicillin-resistant *Staphylococcus pseudintermedius* (2/36, 5.6%). AKI occurred in 6 of 36 patients (16.7%) during vancomycin treatment but could not definitively be attributed to vancomycin treatment in any patients because of illness severity, additional nephrotoxic treatments, or both. Neutropenia or allergic reaction was not documented in any animal. In 2 of 36 patients (5.6%), susceptibility data documented an infection that was only susceptible to vancomycin. Most patients survived to discharge (25/36, 69.4%).

Conclusions and Clinical Importance: Adverse effects attributable to vancomycin were infrequent in dogs and cats. In most cases, there were potential alternative effective antimicrobials or lack of susceptibility data to support vancomycin treatment.

KEYWORDS

acute renal failure, antibiotic resistance, antibiotic stewardship, glycopeptide

1 | INTRODUCTION

The introduction of vancomycin in the 1950s had substantial impact on the outcome of treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in human patients. Vancomycin is a glycopeptide antimicrobial derived from the actinomycete *Streptomyces orientalis* which displays time-dependent bactericidal activity against the most susceptible organisms by activating bacterial cell wall autolysins, as well as bacteriostatic activity against enterococci by binding to the D-alanyl-D-alanine portion of cell wall precursors.[1,2] The spectrum of activity of vancomycin includes *Streptococcus*, *Enterococcus*, and *Staphylococcus* (including MRSA and methicillin-resistant *Staphylococcus pseudintermedius* [MRSP]). It is not effective against Gram-negative bacteria. Oral administration of vancomycin results in virtually undetectable serum concentrations in people; therefore, it must be given parenterally to

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treat systemic infections. PO-administered vancomycin however is widely utilized in people for localized treatment of *Clostridium difficile* enteric infections and prophylaxis.[3,4]

Acquisition of resistance mechanisms by bacterial organisms allows for amplification and propagation in human and animal populations.[5,6] Pathogenic *Staphylococcus* is prevalent in a variety of companion animals,[7–9] and data show bidirectional transmission between companion animals and people,[9,10] indicating a clinically important zoonotic risk.

In people, vancomycin dosing is based on patient weight and creatinine clearance guided by daily therapeutic drug monitoring to avoid accumulation and toxicity.[11,12] Potential adverse effects of vancomycin administration in people include nephrotoxicity, ototoxicity, neutropenia, and "red man syndrome," characterized by vasodilatation, flushing, and hypotension caused by histamine release from mast cells after rapid administration (>10 mg/min).[1,13] Vancomycin-induced kidney injury in people is suspected to be caused by impurities in the vancomycin preparation or coadministration with other nephrotoxic drugs (such as aminoglycosides), because more recent reports have shown fewer cases of nephrotoxicity with vancomycin monotherapy.[2]

The use of IV vancomycin in cats,[14,15] pharmacokinetics in dogs,[16] and systemic use in horses[17] is reported in the veterinary literature, but clinical data documenting the parenteral use of vancomycin for naturally occurring infections are needed in small animal veterinary patients. Successful clinical outcomes in dogs with vancomycin-susceptible infections are limited to several case reports.[18–20] One case series reported 2 dogs that were inappropriately treated with PO vancomycin for severe soft tissue infections, highlighting the lack of familiarity and standardization of vancomycin administration in small animal practice.[21] Guidelines for prudent use of vancomycin to prevent vancomycin-resistant infections[22] as well as for appropriate treatment of MRSA organisms[23] are well established in people. Several veterinary expert groups have published evidence-based recommendations for responsible use of antimicrobials[24,25] including MRSA and MRSP infections,[25] and support is growing for restriction of glycopeptides such as vancomycin.

Our objective was to evaluate parenterally administered vancomycin in dogs and cats. The main aims were to describe the types of infections, clinical outcomes of patients and to report adverse events in patients treated with vancomycin.

2 | MATERIALS AND METHODS

2.1 | Data collection

Electronic medical records of the Foster Hospital for Small Animals at Tufts University were searched to identify all dogs and cats that were treated with vancomycin at any dosage or duration between January 2003 and October 2017. Patients were included in the study if vancomycin was administered and the medical record was available for review. To decrease selection bias, individual patients that were treated with vancomycin during >1 hospitalization were counted only once, with cumulative data reviewed in regard to duration of treatment and evidence of adverse effects.

The following variables were collected from the medical record: species, breed, age, weight, dosage and frequency of vancomycin administered, total number of doses received, and source of infection targeted by vancomycin treatment. Infections detected after 48 hours of hospitalization, within 3 days of discharge from a veterinary hospital, or within 30 days of a surgical procedure were defined as hospital-associated infections (HAI) for the purpose of the study.[26] Sepsis was defined based on histological, microbiological, gross confirmation (purulent exudate with intracellular bacterial organisms identified) of infection (except in patients with pneumonia, in which radiographic evidence or computed tomography was acceptable), and evidence of systemic illness based on fulfillment of ≥2/4 or ≥3/4 of the systemic inflammatory response syndrome (SIRS) criteria, respectively, for dogs and cats, as described previously.[27,28] Patients that met SIRS criteria but had no documented infection were categorized as noninfectious SIRS (NSIRS). Patients were categorized as having developed acute kidney injury (AKI) after initiation of vancomycin treatment based on the International Renal Interest Society AKI guidelines.[29]

The suspected or confirmed primary source of infection was recorded for each case. Source of infection was categorized as integument in the case of fasciitis, bite or burn wounds, or infected skin masses. We attempted to determine the specific target infection for vancomycin administration from the medical records. If unclear or not specifically stated in the record, the source of infection was listed as "undetermined." The ability to de-escalate treatment for an infection was considered present if a positive culture was obtained and susceptibility existed to any other commonly prescribed antimicrobial besides vancomycin. When another effective antimicrobial was noted in the susceptibility data, it was noted whether de-escalation occurred (defined as discontinuation of vancomycin in ≤24 hours after culture and susceptibility data were finalized). Delayed de-escalation was defined as discontinuation of vancomycin in >24 hours after culture data were finalized. No de-escalation was defined as continued vancomycin administration after susceptibility data were finalized and until the time of discharge.

2.2 | Data analysis

Descriptive statistics are presented. Continuous data are reported as median and range subgrouped by species. Categorical and binary data are reported as proportions subgrouped by species. Statistical comparisons were not performed on these data because of the heterogenous nature of the data and limited number of dogs and cats enrolled. Long-term outcome data are represented by a Kaplan-Meier curve, generated by commercial software (Excel 2017, Microsoft Corp, Redmond, Washington).

3 | RESULTS

3.1 | Population data

After entering the search criteria into the Foster Hospital for Small Animals electronic medical record database, 43 individual animals were identified between January 2003 and October 2017. A total of

7 cases was excluded: 1 animal received an intraocular dose, 1 received a local infusion after explant of an orthopedic implant, 2 had incomplete records, and 3 had vancomycin mentioned in the medical record without ever having had it prescribed. One cat and 2 dogs each were treated with vancomycin twice. One of these animals treated twice had the 2nd course of treatment restarted within 7 days of discharge. The other 2 animals had a 2nd course of treatment within 2 months after discharge. One additional dog was hospitalized and treated 3 times, the interval between each course of treatment being within 10 days of previous discontinuation. Seven of the 36 (19.4%) animals were cats, and the remaining 29 (80.5%) were dogs. These patients represent 0.10% (7/6746) and 0.12% (29/24382) of the total hospitalized feline and canine inpatients during the study period, respectively. This is equivalent to 1.03 uses of vancomycin per 1000 feline patients and 1.19 uses of vancomycin per 1000 canine patients. The median age during treatment was 8 years old for both dogs and cats. Baseline descriptive patient signalment data including doses of vancomycin and short-term and long-term outcome are presented in Table 1.

The suspected or confirmed source of primary infection is described in Table 2. These data represent the infection for which the patient was originally hospitalized, not necessarily the infection for which vancomycin was prescribed. Because of the retrospective nature of this research and the fact that many patients had multiple possible infection sites on differential diagnosis lists, the infection targeted by vancomycin treatment was not always clear from the medical record. Therefore, the site of infection for which the patient was hospitalized was reported. Twenty-nine cases (29/36, 80.6%) met the criteria for sepsis at the time of initiation of vancomycin treatment. Of the 7 animals that received vancomycin but did not fit sepsis criteria, 5 (5/36, 13.9%) had resistant infections documented by culture results without meeting SIRS criteria and 2 (2/36, 5.6%) were categorized as NSIRS. One dog that met the criteria for NSIRS was suspected to have bacteremia but had negative culture results. Another dog categorized as NSIRS was tentatively diagnosed with septic fasciitis and possible aspiration pneumonia with documented febrile neutropenia but had negative SC tissue and blood cultures and also had recently received carboplatin for pulmonary adenocarcinoma and chemotherapy-associated myelosuppression without sepsis could not be ruled out. In summary, the majority of patients (34/36, 94.4%) had an infection documented by positive culture results from any source during hospitalization. All animals (36/36, 100%) were treated with >1 antibiotic during their hospitalization.

Vancomycin treatment was initiated empirically in the majority of patients (24/36, 66.7%), whereas a smaller percentage of treatments was based on preliminary or confirmed culture data (9/36, 25.0%). Twenty-six patients had finalized culture results before death or discharge. Of these, 24 of the 26 (92.3%) patients could have been de-escalated to another antibiotic. For 2 of the 26 cases (7.7%), vancomycin was the only antibiotic to which the organism was susceptible based on culture data, which represents 5.6% (2/36) of all animals treated. In those cases in which de-escalation was possible, immediate de-escalation occurred in 8 of 24 (33.3%) and delayed de-escalation occurred in 5 of 24 (20.8%) cases. No de-escalation of vancomycin was noted before discharge in 11 of the 24 cases (45.8%).

Based on the medical records, vancomycin treatment was started because of suspected or confirmed HAI in 24 of 36 (66.7%) cases, 16 of 24 (66.7%) of which were definitively confirmed by positive culture. One dog was diagnosed with in-hospital acquired aspiration pneumonia based on a witnessed aspiration event, radiographic pulmonary infiltrates, and new-onset fever, but no culture (ie, by endotracheal wash) was performed. Thus, 17 HAIs were diagnosed (17/36, 47.2% of all patients). Sources of HAI included indwelling urinary catheters, orthopedic implants, wound or incisional contamination, in-hospital aspiration pneumonia, and central line-associated bacteremia (Table 3). Most HAIs confirmed on culture indicated susceptibility of the infectious organism to several antibiotics (8/16, 50%), susceptibility to chloramphenicol at minimum (5/16, 31.3%), or susceptibility to trimethoprim/sulfomethoxazole at minimum (2/16, 12.5%). Vancomycin was the only antibiotic to which the organism was susceptible in 1 patient (1/16, 6.25%) with culture-confirmed HAI (a cat with an indwelling catheter-associated urinary tract infection). The HAIs treated with vancomycin for which culture and susceptibility data were available were caused by *Enterococcus* sp. (5/16, 31.3%), MRSA (6/16, 37.5%), MRSP (2/16, 12.5%), *Staphylococcus* sp. (1/16, 6.25%), *Enterococcus* sp. and MRSA coinfection (1/16, 6.25%), or *Enterococcus* sp. and *Staphylococcus* sp. coinfection (1/16, 6.25%).

Vascular access devices or multi-lumen venous catheters were left in place for at-home vancomycin administration in 6 of 36 patients (16.7%). The overall rate of initial discharge from the hospital was 69.4% (25/36 cases). Six patients were euthanized (16.7%) and 5 patients suffered cardiopulmonary arrest (13.9%). Of the 26 patients that survived to initial discharge, at least 3 patients (3/26, 11.5%) were known to have been euthanized within 7 days of discharge, but 4 of the 26 (15.4%) patients were lost to follow-up. Thus, the maximum overall rate of survival >7 days after discharge was 61.1% (22/36 patients). The maximum long-term survival after discontinuation of vancomycin based on available follow-up records (as a Kaplan-Meier curve) is presented in Figure 1.

3.2 | Vancomycin data

The most commonly prescribed starting dosage of vancomycin was 15 mg/kg IV q6h (22/36 cases, 61.1%), but there was considerable variation (see Table 4). In 6 of 36 cases (16.7%), the initial starting dose or dosing frequency was altered at some point during the course of treatment. A reason for altered dosing was not clear from any of the records reviewed. For 1 patient (receiving 12.5 mg/kg IV q6h), the record stated that this dosage was chosen as an estimated decreased dose based on the patient's baseline serum creatinine concentration, but the patient only received 1 dose of vancomycin and creatinine clearance was not measured. Only 1 patient (1/36, 2.8%) had a vancomycin serum trough concentration determined. It was determined at the time of discontinuation of vancomycin because of AKI detected on day 23 of treatment, but the result of the trough concentration was not reported in the record. Number of vancomycin doses and data regarding outpatient treatment by indwelling IV catheters are presented in Table 1.

Overall patient adverse events detected are summarized in Table 5. Four animals (4/36, 11.1%) had neutropenia documented during their hospitalization, but all instances were before vancomycin

TABLE 1   Baseline descriptive patient data of 29 dogs and 7 cats treated with IV vancomycin from January 1, 2003 to October 31, 2017

Characteristic	Dogs N = 29 (%)	Cats N = 7 (%)	Total N = 36 (%)
Sex			
Neutered male	15 (51.7)	4 (57.1)	10 (52.8)
Spayed female	9 (31.0)	3 (42.9)	12 (33.3)
Intact male	5 (17.2)	0 (0.0)	5 (13.9)
Intact female	0 (0.0)	0 (0.0)	0 (0.0)
Breed			
Domestic short/long hair		6 (85.7)	6 (16.7)
Siamese		1 (14.3)	1 (2.8)
Labrador Retriever or Lab mix	6 (20.7)		6 (16.7)
German Shepherd dog	3 (10.3)		3 (8.3)
Bullmastiff	2 (6.9)		2 (5.6)
Pug	2 (6.9)		2 (5.6)
Other (dog)	16 (55.2)		16 (44.4)
Age (y)	8 (3-16)	8 (2-14)	8 (2-16)
No. of vancomycin doses	15 (1-522)	27 (10-76)	15.5 (1-522)
Systemic illness			
Sepsis	25 (86.2)	4 (57.1)	29 (80.6)
NSIRS	2 (6.9)	0 (0.0)	2 (5.6)
Neither	2 (6.9)	3 (42.9)	5 (13.9)
Culture results			
Positive culture susceptible to vancomycin	19 (65.5)	5 (71.4)	24 (66.7)
Enterococcus sp.	8 (27.6)	3 (42.9)	11 (30.6)
MRSP	2 (6.9)	0 (0.0)	2 (5.6)
MRSA	6 (20.7)	2 (28.6)	8 (22.2)
Staphylococcus sp.	1 (3.4)	0 (0.0)	1 (2.8)
Staphylococcus sp. and *Enterococcus* sp.	2 (6.9)	0 (0.0)	2 (5.6)
Positive culture, vancomycin not reported	8 (27.6)	2 (28.6)	10 (27.8)
Positive culture resistant to vancomycin	0 (0.0)	0 (0.0)	0 (0.0)
Negative culture	2 (6.9)	0 (0.0)	2 (5.6)
Treatment location			
In-hospital only	24 (82.8)	6 (85.7)	30 (83.3)
In-hospital and at home	5 (17.2)	1 (14.3)	6 (16.7)
Short-term outcome			
Discharged	20 (69.0)	5 (71.4)	25 (69.4)
Died	5 (17.2)	0 (0.0)	5 (13.9)
Euthanized	4 (13.8)	2 (28.6)	6 (16.7)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MRSP, methicillin-resistant *Staphylococcus pseudintermedius*; NSIRS, non-infectious systemic inflammatory response syndrome; SIRS, systemic inflammatory response syndrome.

Breed proportions are reported as percentages of totals within the same species. Culture data represent all culture/susceptibility data available during hospitalization(s) for which IV vancomycin was administered. Values are reported for number of dogs and cats, median (range), or number (%). Age was rounded to the nearest integer. Dogs whose breed was classified as "other" included 1 dog from each of the following breeds: Shar Pei, St. Bernard, Cairn Terrier, Tibetan Terrier, Border Collie, Basset Hound, Golden Retriever, Bull Terrier, Great Pyrenees, Bichon Frise, Lhasa Apso, English Setter, Cocker Spaniel, Rat Terrier, Schnauzer mix, Rottweiler.

The sepsis category includes only cats and dogs that fulfilled sepsis criteria at the time of vancomycin initiation. Sepsis was defined as fulfillment of species-specific SIRS criteria and evidence of infection. Specific SIRS criteria for dogs included abnormal body temperature (<100.6°F or >102.6°F), tachycardia (HR > 120 bpm), tachypnea (>40 breaths/min), and abnormal leukogram (WBC count <6 × 10³/μL or >16 × 10³/μL or >3% bands). For cats, SIRS criteria were defined as abnormal body temperature (<100°F or >103.5°F), abnormal heart rate (HR < 140 bpm or >225 bpm), tachypnea (>40 breaths/min), and abnormal leukogram (WBC count <5 × 10³/μL or >19.5 × 10³/μL or >5% bands).

administration. Normal or increased neutrophil counts were documented in 50.0% (18/36) of patients, but a CBC was not evaluated in many instances (14/36, 38.9%). No allergic reactions characterized by hyperemia, vasodilatation, or hypotension were reported, but 8 of 36 animals (22.2%) had phlebitis or other local tissue irritation noted at the area of IV administration of vancomycin.

No evidence of AKI was identified after starting vancomycin in 21 animals (58.3%). In 7 patients (7/36, 19.4%), AKI was not clinically suspected based on evaluation of their medical records, although urine output, renal blood testing, or both was not regularly performed. One (1/36, 2.8%) patient had prerenal azotemia that resolved before vancomycin administration and another patient (1/36, 2.8%) had

TABLE 2 Suspected or confirmed primary sources of infections in hospitalized cats and dogs treated with IV vancomycin

Source of infection	Dog N = 29 (%)	Cat N = 7 (%)	Total N = 36 (%)
Integument	7 (21.4)	3 (42.9)	10 (27.8)
Hepatobiliary	5 (17.2)	2 (28.6)	7 (19.4)
Orthopedic implant	5 (17.2)	0 (0.0)	5 (13.9)
Gastrointestinal	4 (13.8)	1 (14.3)	5 (13.9)
Urinary	3 (10.3)	1 (14.3)	4 (11.1)
Endocarditis	3 (10.3)	0 (0.0)	3 (8.3)
Respiratory	1 (3.4)	0 (0.0)	1 (2.8)
Osteomyelitis	1 (3.4)	0 (0.0)	1 (2.8)

pre-existing mild azotemia that did not progress with vancomycin treatment. Clear evidence of AKI was noted in 6 of 36 patients (16.7%), only 1 of which survived to discharge. The surviving patient developed AKI after 21 days of vancomycin treatment and had gradual but complete return to baseline serum creatinine concentration after 2 months. It is unknown whether this patient developed evidence of long-term renal insufficiency. The remaining 5 patients developed AKI between 12 hours and 4 days after starting treatment with vancomycin, and all either developed cardiopulmonary arrest or were euthanized because of the severity of their disease. Of 6 patients that developed AKI, 3 (50%) had documented oliguria or anuria.

4 | DISCUSSION

Our study describes the use of IV vancomycin in dogs and cats with naturally occurring infections. The majority of vancomycin prescriptions were empirical despite rare culture evidence of resistance to other commonly prescribed antibiotics. Because of the retrospective nature of our study, the rationale for the empirical use of vancomycin as well as the timing of de-escalation based on susceptibility data could not be fully evaluated. In cases in which vancomycin was used empirically without preliminary or final culture evidence, concern for HAI was the most frequently documented reason for escalation of antimicrobial coverage. Although some records mentioned new onset of fever during hospitalization or concern for methicillin-resistant staphylococcal infections around the time vancomycin treatment was initiated, this was not consistent and often not explicitly stated as the rationale for prescribing vancomycin. The retrospective nature of our

TABLE 3 Sources of hospital-associated infections in cats and dogs treated with IV vancomycin

Source of HAI	Dog N = 29 (%)	Cat N = 7 (%)	Total N = 36 (%)
No HAI	17 (58.6)	3 (42.9)	20 (55.6)
HAI	12 (41.4)	4 (57.1)	16 (44.4)
Contaminated wound/incision	4 (13.8)	2 (28.6)	6 (16.7)
Urinary catheter	2 (6.9)	2 (28.6)	4 (11.1)
Orthopedic implant	4 (13.8)	0 (0.0)	4 (11.1)
Aspiration pneumonia	1 (3.4)	0 (0.0)	1 (2.8)
CLABSI	1 (3.4)	0 (0.0)	1 (2.8)

Abbreviations: CLABSI, central line-associated blood stream infection; HAI, hospital-associated infections.
Percentages reported are out of all HAI (N = 17).
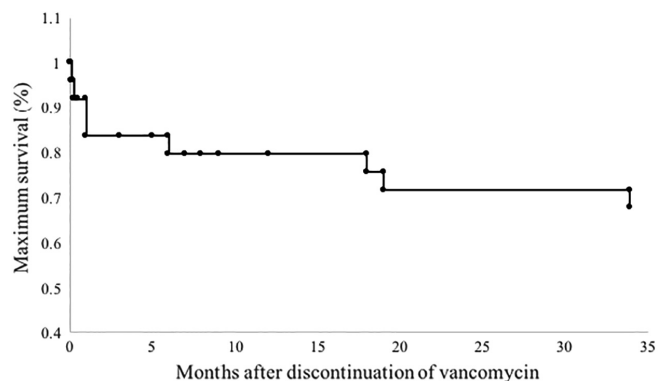
FIGURE 1 Kaplan-Meier curve representing the maximum known long-term survival (in months) after discontinuation of vancomycin based on available follow-up records. Data presented only for those patients which survived to initial discharge from hospital (n = 26)

study limits further discussion of the reasons for delayed or lack of de-escalation.

The use of vancomycin in human hospital settings has escalated markedly since its approval by the United States Food and Drug Administration in 1956 and has been attributed to the increase in nosocomial infections caused by MRSA (from 2% in 1974 to >50% in 2000).[30] Accordingly, there is growing concern about vancomycin resistance as the emergence of community-acquired MRSA isolates (rather than just nosocomial strains) has been better recognized, and both vancomycin-intermediate and vancomycin-resistant *S. aureus* isolates have been increasingly identified. In some cases, the efficacy of vancomycin has been questioned because of clinical failures and high rates of relapse, which has engendered more support for alternative treatments for MRSA infections (eg, linezolid and daptomycin).[31–34] In addition, 1 of the 2 case reports of clinical use of vancomycin in cats showed failure to clear infection despite clinical improvement.[15]

Organisms most frequently cultured from HAIs in our study were similar to those commonly treated with vancomycin in human patients, but cases in which vancomycin was the only appropriate option were rare (2/36, 1 of which was an HAI, 2.8% of all cases treated). In both of these cases, vancomycin was prescribed to treat enterococcal organisms that were part of a polymicrobial infection. Enterococcal infections pose a unique treatment dilemma in that both *Enterococcus faecalis* and *Enterococcus faecium* are important contributors to HAIs and are often highly resistant, but data in human medicine suggest that they do not always require treatment when

TABLE 4 Initial dosage and frequency of vancomycin administration in 29 dogs and 7 cats treated between January 1, 2003 and October 31, 2017

Dose administered	Dog N = 29 (%)	Cat N = 7 (%)	Total N = 36 (%)
15 mg/kg IV q6h	19 (65.5)	3 (42.9)	22 (61.1)
15 mg/kg IV q8h	5 (17.2)	3 (42.9)	8 (22.2)
15 mg/kg IV q12h	1 (3.4)	0 (0.0)	1 (2.8)
15 mg/kg IV q24h	1 (3.4)	0 (0.0)	1 (2.8)
12.5 mg/kg IV q6h	1 (3.4)	1 (14.3)	2 (5.6)
11 mg/kg IV q6h	1 (3.4)	0 (0.0)	1 (2.8)
7.5 mg/kg IV q6h	1 (3.4)	0 (0.0)	1 (2.8)

TABLE 5 Adverse effects in 29 dogs and 7 cats treated with IV vancomycin from January 1, 2003 to October 31, 2017

Adverse effect	Dogs N = 29 (%)	Cats N = 7 (%)	Total N = 36 (%)
AKI			
Pre-existing	2 (6.9)	0 (0.0)	2 (5.6)
New	5 (17.2)	1 (14.3)	6 (16.7)
None	17 (58.6)	4 (57.1)	21 (58.3)
Not completely documented	5 (17.2)	2 (28.6)	7 (19.4)
Neutropenia			
Pre-existing	3 (10.3)	1 (14.3)	4 (11.1)
New	0 (0.0)	0 (0.0)	0 (0.0)
None	15 (51.7)	3 (42.9)	18 (50.0)
Not completely documented	11 (37.9)	3 (42.9)	14 (38.9)
Allergic reaction	0 (0.0)	0 (0.0)	0 (0.0)
Phlebitis	7 (24.1)	1 (14/3)	8 (22.2)

Abbreviation: AKI, acute kidney injury.
AKI was defined based on International Renal Interest Society guidelines (an increase in blood creatinine ≥0.3 mg/dL from baseline, oligoanuria, or both defined as <1 mL/kg/h over at least 6 h).

detected as a coinfection with another organism and may resolve with antibiotics targeting the other components of mixed infection.[35] In addition, asymptomatic bacteriuria from multidrug resistant enterococcal colonization is common in hospitalized people who are catheterized and usually does not require treatment.[36] In contrast, resistant enterococcal species are important causes of serious infections such as endocarditis and meningitis in people and can contribute to substantial morbidity and mortality. Some evidence also exists that enterococcal infections are an important cause of postoperative abdominal infections in people.[37] Given the emergence of vancomycin resistance in people and the data presented in our study, it may be prudent to discourage vancomycin treatment for enterococcal infections when cultured as a coinfection. In addition, the susceptibility data reviewed here do not support empirical use of vancomycin for non-enterococcal infections, but it could be considered after full susceptibility data are available on a case-by-case basis.

In people, vancomycin-induced neutropenia, defined as absolute neutrophil counts <1000/μL, is reported in 2%-12% of treated patients and is related to duration of treatment (>7 days, with most cases occurring beyond day 20 of treatment), rather than daily doses, total cumulative doses, or incidence of supratherapeutic serum vancomycin concentrations.[38] No suspected cases of vancomycin-associated neutropenia were identified in our study, but most animals (18/36, 50.0%) were noted to either have pre-existing neutropenia or no documentation of a CBC performed after the start of treatment. In addition, only 6 animals were treated with vancomycin for ≥20 days. Interestingly, 1 patient was treated continuously for >5 months after developing recurrent bacteremia after initial treatment was discontinued, but never developed neutropenia on subsequent CBCs.

Nephrotoxicity attributed to vancomycin use initially was seen when it was first isolated in the 1950s, but subsequent studies have shown that newer formulations tested in the 1970s produced far less kidney damage, although the risk is greater with concurrent administration of aminoglycosides[39] or when administered in very high doses.[40] A recent meta-analysis in people has shown some evidence

of the specific combination of vancomycin with piperacillin-tazobactam as having an association with higher rates of AKI when compared to vancomycin monotherapy, but specific prospective data are lacking.[41] The absolute risk of vancomycin-induced AKI is likely multifactorial and patient specific. The risk of vancomycin-induced nephrotoxicity may be higher in those that receive higher doses, longer duration of treatment, those concurrently treated with other drugs that have nephrotoxic potential, or in critically ill patients susceptible to poor renal perfusion.[42] In our study, 6 of 36 patients (16.7%) had documented AKI after starting vancomycin treatment. Five of these patients developed AKI between 0.5 and 4 days after starting vancomycin. Although illness severity scoring could not be objectively determined retrospectively, at the time of newly documented AKI, 5 of 5 were septic and 4 of 5 patients had evidence of multiple organ dysfunction. Specifically, these patients all had concurrent hyperbilirubinemia and new onset hypoxemia requiring oxygen treatment, 2 (2/4) were both coagulopathic and thrombocytopenic, and 1 patient had vasopressor-dependent hypotension. In addition, these 4 patients were being concurrently treated with at least 1 other medication or treatment that has been associated with AKI or nephrotoxicity in cats and dogs, such as systemic aminoglycosides, colloid fluids, diuretics, or some combination of these. The other patient (1/5) also was hypotensive, bradycardic, and hypoglycemic at the time of AKI diagnosis. Given these limitations, conclusions as to whether AKI development was related to vancomycin treatment are confounded by the patient's underlying disease and concurrent medical treatments. None of these 5 patients survived to discharge.

One dog treated with vancomycin for aortic valve endocarditis developed AKI after 21 days of vancomycin treatment (blood urea nitrogen [BUN] concentration, 88 mg/dL; serum creatinine concentration, 3.1 mg/dL increased from baseline values of 9 and 1.2 mg/dL, respectively). Although the patient was clinically doing well at the time of 1st documentation of AKI based on azotemia, within 1-2 days the animal developed lethargy and anorexia. The patient had evidence of disease processes that also could have contributed to AKI, such as cylindruria without azotemia 1 month before while being treated with amikacin, hypercoagulability based on thromboelastography testing, and evidence of pulmonary thromboembolism on echocardiography. Although the patient's renal test results returned to within the normal reference range 1 month after discontinuing vancomycin (BUN concentration, 11 mg/dL; serum creatinine concentration, 0.8 mg/dL), we are unable to determine a specific underlying cause of AKI. Interestingly, 5 of 6 animals that developed AKI were treated with the highest dosage and frequency administered (15 mg/kg q6h), but variable diagnostic renal testing and small sample size precluded further statistical analysis of this cohort.

Dosing regimens for IV vancomycin in people are largely impacted by the patient's creatinine clearance and adjusted by body weight and then titrated based on serum peak and trough vancomycin concentrations after the 4th dose, based on pharmacokinetic studies.[13,43] In people, substantial evidence indicates that certain disease states such as sepsis or septic shock can alter serum drug concentrations. This is highly dependent on the patient's vascular permeability and subsequent alteration of volume of distribution and target organ concentration and organ dysfunction, which alters drug clearance. For

hydrophilic antibiotics such as the glycopeptides, fluid shifts can cause increased volume of distribution, which leads to a decreased maximum serum drug concentration, whereas renal dysfunction tends to increase serum drug concentrations because of decreased clearance. Because this is difficult to quantify at the bedside, therapeutic drug monitoring and dose adjustment (usually in conjunction with a clinical pharmacist) are required to avoid subtherapeutic dosing.[43,44] This approach is recommended in a recent consensus statement by infectious disease specialists in human medicine.[44] Monitoring trough drug concentrations was found to be essential in avoiding vancomycin resistance from subtherapeutic dosing, but routine measurement of peak vancomycin concentrations could not be recommended because of conflicting evidence regarding the association of vancomycin blood levels and incidence of adverse effects.[44] To the best of our knowledge, no therapeutic drug monitoring studies have been conducted in dogs and cats. Based on the available evidence, therapeutic drug monitoring is recommended in small animal patients requiring vancomycin and is likely important in preventing development of resistance from suboptimal dosing.

In our study, therapeutic drug monitoring was not completed in any patient. One patient was noted to have a drug trough concentration submitted, but the result was not recorded (performed at an outside laboratory). A pharmacokinetic study of IV vancomycin administration in healthy adult dogs at a dosage of 15 mg/kg q12h for 10 days indicated that the mean elimination half-life was approximately 137 minutes (standard deviation [SD], 21.8 minutes) after a single dose and was decreased to a mean of 104 minutes (SD, 11.2 minutes) by the final dose.[16] A dosage of 15 mg/kg q6h-q8h has been suggested based on this data and is probably appropriate for relatively healthy dogs. Given the variable dosing intervals in dogs in our study, those dosed at lower frequencies (q12h-q24h) may have had subtherapeutic serum drug concentrations depending on the patient's vascular integrity and renal function. To the best of our knowledge, no pharmacokinetic data are available in cats. Given the retrospective nature of our study and the likely variable degree of organ dysfunction among patients or within the same patient at different stages of their hospitalization, we cannot determine what dosing may be optimal for patients with naturally occurring infection.

Our study had important limitations, many of which are a consequence of its small sample size and retrospective nature. Precise reasons for prescribing and treatment decisions such as dose and frequency of administration or immediate versus delayed de-escalation practices were not always apparent from review of the medical records. Our study represents cases from a tertiary facility, which may not be similar to prescribing patterns or type of cases seen at other veterinary facilities. Rates of adverse effects from vancomycin may be underreported because of the lack of uniform monitoring (eg, neutropenia, hypotension, and AKI) in our retrospective study. Many patients were lost to follow-up, limiting conclusions about successful treatment of infections. Finally, the population studied was not homogeneous in nature, making it difficult to draw conclusions about vancomycin use in specific types of infections or subpopulations.

In conclusion, vancomycin administration in dogs and cats for life-threatening infections was generally well tolerated, but additional prospective studies are needed to further evaluate the risk of AKI. Based on culture and susceptibility data in this specific population of dogs and cats, treatment with vancomycin rarely was necessary. Restriction of use to only patients with culture evidence of susceptibility that lack reasonable other antimicrobial options is warranted, which is in agreement with a recently published antimicrobial stewardship policy outlined by the American Veterinary Medical Association.[45] Further research regarding therapeutic drug monitoring to guide vancomycin treatment and its effects on prevention of antimicrobial resistance and adverse effects in veterinary species is warranted.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

This study retrospectively evaluated the off-label use of vancomycin in dogs and cats.

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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