

Escherichia coli isolated from canine pyometra show decreased susceptibility to amoxicillin-clavulanic acid in dogs

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Objective

To describe bacterial culture results and antimicrobial susceptibility patterns for dogs undergoing surgical treatment for pyometra.

Methods

This retrospective study included dogs that underwent ovariohysterectomy at referral hospitals and had a positive bacterial culture of uterine fluid or histopathologic changes consistent with pyometra between January 2020 and December 2024. Data collected from medical records included clinical signs on presentation, hematological and biochemical abnormalities, aerobic and anaerobic bacterial isolates, antimicrobial susceptibility results, and peri- and postoperative antimicrobial administration. Prevalence of antimicrobial susceptibility was compared across select geographic regions and between Clinical and Laboratory Standards Institute (CLSI) susceptibility interpretation guideline editions.

Results

278 dogs were included. Neutrophilia was identified in 74.2% of dogs. Only 1 bacterium was isolated in 88.8% of dogs, while 10.4% of cases were polymicrobial. *Escherichia coli* was the most common isolate (73.1%). Amoxicillin-clavulanic acid and enrofloxacin were prescribed postoperatively to 77.6% and 51.1% of dogs, respectively. Using CLSI VET01S edition 4, *E coli* susceptibility to amoxicillin-clavulanic acid and enrofloxacin was present in 30.3% and 96.9% of isolates, respectively. Reclassification using CLSI VET01S edition 7 resulted in lower susceptibility classifications in 9 of 10 antimicrobials evaluated, including reductions of 46.9% for amoxicillin-clavulanic acid and 3.1% for enrofloxacin.

Conclusions

Amoxicillin-clavulanic acid was frequently prescribed despite limited susceptibility among *E coli* isolates. Updated CLSI breakpoints reclassified susceptibility for most antimicrobials despite unchanged MICs.

Clinical Relevance

Regional antibiograms may show decreased susceptibility compared to historical recommendations. Judicious empiric antimicrobial selection should be guided by antimicrobial stewardship principles rather than routine reliance on any single antimicrobial.

Keywords: amoxicillin-clavulanic acid, antimicrobial resistance, antimicrobial susceptibility testing, *Escherichia coli*, pyometra

Pyometra, a bacterial infection of the uterus, is diagnosed in up to 23% of intact bitches by 10 years of age.^{1,2} This hormonally mediated disease occurs in diestrus, during which elevated progesterone concentrations stimulate endometrial hyperplasia and cystic glandular secretion. Reduction in uterine contractility and suppression of local immune defenses increase susceptibility to ascending infection, resulting in the accumulation of purulent intrauterine fluid.^{3,4} Gram-negative bacterial

isolates predominate, with *Escherichia coli* identified in approximately 66% to 90% of cases.⁵⁻⁷

Common clinical signs include vomiting, polydipsia/polyuria, abdominal pain, and dehydration.^{8,9} Vaginal discharge may be present, indicating cervical patency.^{10,11} Anemia, thrombocytopenia, hypoalbuminemia, and azotemia have also been reported.⁸ Without timely treatment, uterine rupture, septic peritonitis, and death can occur.^{8,12}

While medical management has been described, ovariohysterectomy (OVH), in combination with antimicrobial therapy, remains the treatment of choice for pyometra among both primary and specialty care veterinarians in the US.^{13,14} In both surgical and medical treatment, broad-spectrum antimicrobials

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are often prescribed empirically; ampicillin, amoxicillin-clavulanic acid (AMC), enrofloxacin, and a cephalosporin have been recommended.^{4,15} Antimicrobial selection should be based on expected pathogen susceptibility patterns and subsequently adjusted according to culture and antimicrobial susceptibility testing results.⁵

Antimicrobial resistance (AMR) in *E coli* infections has increased in recent years, with multiple veterinary studies reporting resistance to amoxicillin and its derivatives.^{5,16–18} These findings mirror trends observed in human medicine, in which multidrug resistance (MDR) in *E coli* has increased significantly over the last decade,^{19,20} raising concerns regarding ongoing and progressive AMR and reduced antimicrobial efficacy.

Antimicrobial resistance arises from selection pressure associated with antimicrobial use, with overuse and misuse of empiric therapy representing key drivers.¹⁹ Geographic variability in AMR has been documented in both human and veterinary medicine, suggesting regional clustering of resistant phenotypes and highlighting the importance of location-specific data to guide empiric therapy and reduce the risk of ineffective treatment.^{17,21,22} If possible, an empiric antimicrobial agent with at least 80% susceptibility of the anticipated organism should be chosen.²³ However, AMR data and disease-specific antibiograms to inform empiric decisions remain limited for many conditions, including canine pyometra.^{16,17}

As veterinary antimicrobial susceptibility testing interpretations published by the Clinical and Laboratory Standards Institute (CLSI) continue to evolve, empiric antimicrobial recommendations for canine pyometra in older veterinary literature may not fully align with current CLSI guidelines. Given the reliance on initial empiric antimicrobial therapy, understanding current antimicrobial susceptibility patterns (ASPs) within the context of evolving CLSI interpretive criteria may help guide more effective treatment.

The primary objective of this study was to describe uterine bacterial culture results and ASPs in dogs with pyometra treated by OVH in the US using a standardized interpretation of raw MIC data. As a secondary objective, we sought to evaluate how evolving CLSI breakpoint criteria influence antimicrobial susceptibility interpretations by comparing the same MIC data for pyometra bacterial isolates using the CLSI VET01S edition in use during the majority of the study period (edition 4)²⁴ and the current edition (edition 7).²⁵ We hypothesized that, when interpreted using CLSI VET01S edition 4, there would be lower susceptibility of *E coli* to AMC compared to enrofloxacin and that AMC susceptibility would remain below the CLSI-recommended 80% threshold for empiric antimicrobial selection, suggesting it represents a suboptimal empiric antimicrobial choice for canine pyometra. We further hypothesized that reinterpretation of the same MIC data using CLSI VET01S edition 7 would result in lower reported susceptibility to selected antimicrobials, despite no change in the underlying MIC values.

Methods

Case inclusion

Electronic medical record databases of 16 referral hospitals in the US were retrospectively reviewed to identify dogs with pyometra undergoing OVH between January 2020 and December 2024.

Dogs were included if a culture of uterine contents was submitted at the time of OVH for pyometra. If there was no growth on bacterial culture, dogs were included if uterine tissue was submitted for histopathology and changes consistent with pyometra were present. Samples were submitted to reference laboratories according to the individual hospital protocols. The MICs of the antimicrobial susceptibility reports were collected. Dogs with stump pyometra were included if remaining ovarian tissue was present at the time of surgery.

Medical record review

Information obtained from the medical records included breed, age, body weight, clinical signs and duration thereof, length of time since last estrus, and physical examination findings. Specific clinical signs that were tabulated included vomiting, inappetence, lethargy, and polyuria/polydipsia. Physical examination findings recorded included abdominal pain, vaginal discharge, and dehydration level. The results of vaginal cytology, if performed, were noted. Hematological and biochemical abnormalities were recorded. Anemia was defined as Hct or PCV < 35%. Neutrophilia was defined as neutrophil count > 11.64×10^3 cells/ μ L. Presence of left shift was not assessed owing to incomplete documentation of this parameter in available medical records. Thrombocytopenia was defined as a platelet count < 120×10^3 / μ L. Azotemia was defined as elevation of serum creatinine (> 1.9 mg/dL) or BUN level (> 27 mg/dL). Hypoalbuminemia was defined as serum albumin < 2.5 g/dL. Using systemic inflammatory response syndrome (SIRS) as a potential marker of sepsis, dogs were scored according to the SIRS criteria described by Spillane et al.²⁶ Dogs meeting ≥ 2 of 4 criteria (temperature, heart rate, respiratory rate, and leukogram abnormalities) were classified as positive for SIRS. Survival to discharge was noted. Length of hospitalization was defined as the number of days from admission to discharge or death for nonsurvivors. If histopathological examination of the uterus was performed, results thereof were included.

Antimicrobial use

Preoperative antimicrobial therapy was defined as antimicrobial administration > 2 hours prior to surgical intervention. Perioperative antimicrobial therapy encompassed the intervening time between 2 hours preoperatively and 24 hours postoperatively. Postoperative antimicrobial therapy was defined as oral antimicrobial therapy administered > 24 hours after surgery and continued after hospital discharge. Type of pre-, peri-, and postoperative antimicrobial treatment and the length of postoperative treatment were recorded.

Antimicrobial susceptibility testing

Bacterial species and raw MIC were extracted from the laboratory antimicrobial susceptibility results. To standardize susceptibility interpretation across laboratories and throughout the study period, all MIC values were retrospectively interpreted using both CLSI VET01S edition 4, which was in use during most of the study period and best reflects the susceptibility information available to clinicians when treatment decisions were made, and the current CLSI VET01S edition 7 breakpoint criteria.^{24,25} Susceptibility proportions were calculated separately for each edition. Resistance was defined as non-susceptibility to the antimicrobial. Three laboratories performed antimicrobial susceptibility testing: laboratory A (132 samples; 49 in the Northeast [NE], 50 in the Midwest [MW], and 33 in California [CA]), laboratory B (145 samples; 110 in NE, 28 in MW, and 7 in CA), and laboratory C (1 in MW). Different antimicrobial panels were employed by different laboratories, resulting in varying totals. Median MIC values were calculated for each *E coli*-antimicrobial combination. Susceptibility percentage was reported as number of susceptible isolates per reported antimicrobial. Regional antibiograms for the most common bacterial isolates were created.

Postoperative antimicrobial prescribing

Postoperative antimicrobial prescriptions were compared with antimicrobial susceptibility results generated with the use of standardized interpretation of MIC values using VET01S edition 4. The same MIC data were subsequently interpreted using VET01S edition 7, evaluating for the influence of evolving breakpoint criteria on isolates nonsusceptible to postoperative antimicrobials.

Statistical analysis

All statistical analyses were performed in Prism, version 10.2.3 (GraphPad Software). Age, clinical signs, number surviving to discharge, number of bacterial isolates, histopathology results, preculture antibiotic use, antimicrobial susceptibility results, postoperative antibiotic prescription, and ASPs by bacteria and region were tabulated. Median MICs were calculated for each organism-antimicrobial combination. Susceptibility proportions were calculated separately using VET01S editions 4 and 7. Age and clinicopathologic findings failed the Shapiro-Wilk test for normality ($P < .05$) and are reported as medians with ranges. Geographical differences in susceptibility to AMC and enrofloxacin were evaluated using VET01S edition 4. The Fisher exact test was used for regional comparisons. To account for 3 pairwise regional comparisons within each antimicrobial, P values were adjusted with the Holm-Bonferroni method. Adjusted P values are reported.

Results

A total of 666 dogs underwent OVH for suspected pyometra during the study period. Of these, a total of 388 were excluded owing to a lack of bacterial culture ($n = 349$), combined no growth on bacterial

culture and uterine histopathologic changes consistent with pyometra (32), submission of urine culture only (4), culture results not available for review (2), and cancellation of culture due to patient death prior to discharge (1). Two hundred seventy-eight dogs met the inclusion criteria.

Signalment

Sixty-two breeds were represented, of which mixed-breed dogs were most common ($n = 76$), followed by Pit Bull Terrier (18), Yorkshire Terrier (17), Labrador Retriever (16), and Chihuahua (14). There were 57 additional breeds with 8 or fewer dogs. The median age was 8 years (range, 1 to 16 years), and the median weight was 17.2 kg (range, 1.4 to 69 kg).

Clinical signs

The most common clinical signs, dehydration level, and duration of signs are presented in **Table 1**. Vaginal discharge consistent with an open cervix was noted in 169 of 278 dogs (60.8%). In-hospital vaginal cytology was performed in 7 dogs, all of which showed neutrophils with intracellular bacteria. Rods were seen in 3 cases, cocci in 1 case, diplococci in 1 case, and both rods and cocci in 1 case. In 1 case, the bacterial morphology was not specified. Systemic inflammatory response syndrome criteria were fulfilled in 253 of 276 dogs (92.0%).

Table 1—Clinical signs and duration in 278 dogs with pyometra.

Variable	No. (%) of dogs
Presenting complaint	
Lethargy	241 (86.6)
Inappetence	236 (84.9)
Vomiting	125 (45.0)
Polyuria/polydipsia	92 (33.1)
Examination findings	
Open cervix	169 (60.8)
Painful abdomen	148 (53.2)
Level of dehydration	
0%	48 (17.3)
5%	135 (48.6)
6%–8%	84 (30.2)
8%–10%	4 (1.4)
Not recorded	7 (2.5)
Length of clinical signs	
1 d	50 (18.0)
2–6 d	145 (52.2)
1 wk	53 (19.1)
2 wk	14 (5.0)
3 wk	8 (2.9)
4 wk	5 (1.8)
6 wk	1 (0.4)
8 wk	1 (0.4)
Not recorded	1 (0.4)

Hematological and biochemical findings

Clinicopathologic findings are summarized in **Table 2**. Neutrophilia was present in 196 of 264 dogs (74.2%), and 62 of 267 dogs (23.2%) were thrombocytopenic. A total of 56 of 278 dogs (20.1%) were azotemic, and 42 of 257 dogs (16.3%) were hypoalbuminemic.

Table 2—Select hematological and biochemical values in 278 dogs with pyometra.

Variable	Median (range)	Reference range	No. (%) below reference range	No. (%) above reference range
Hct/PCV (%) n = 278	40.6 (16.3–69.5)	35.0–45.0	61 (21.9)	74 (26.6)
WBCs ($\times 10^3/\mu\text{L}$) n = 264	24.7 (2.35–272.62)	5.8–16.8	18 (6.8)	190 (72.0)
Neutrophils ($\times 10^3/\mu\text{L}$) n = 264	21.0 (0.27–250.2)	3.0–11.6	10 (3.8)	196 (74.2)
Monocytes ($\times 10^3/\mu\text{L}$) n = 264	1.9 (0.0–24.5)	0.15–1.1	6 (2.3)	176 (66.7)
Platelets ($\times 10^3/\mu\text{L}$) n = 263	217.5 (8–936)	120–412	62 (23.2)	29 (11.0)
Total solids (g/dL) n = 275	7.8 (4.4–11.4)	5.5–7.5	7 (2.5)	160 (58.2)
Albumin (g/dL) n = 257	3.0 (1.5–4.5)	2.5–3.9	42 (16.3)	8 (3.1)
BUN (mg/dL) n = 277	15.6 (4–140)	9–27	51 (18.4)	53 (19.1)
Creatinine (mg/dL) n = 278	0.8 (0.3–5.4)	0.5–1.5	17 (6.1)	32 (11.5)

Hospitalization and survival to discharge

The median length of hospitalization was 1 day (range, 1 to 9 days). Two hundred seventy-two dogs (97.8%) survived to discharge. Of the 6 dogs that did not survive, 4 succumbed to cardiopulmonary arrest, with unsuccessful resuscitation efforts. Two dogs were euthanized, 1 because of suspected development of multiple organ dysfunction syndrome and the other because of preexisting but progressive pulmonary hypertension.

Perioperative antimicrobial administration

After admission to the hospital, preoperative antimicrobials were administered in 225 of 278 dogs (80.9%). Perioperative antimicrobials were administered in 133 of 278 dogs (47.8%). Antimicrobials were administered in both the pre- and perioperative periods in 84 of 278 dogs (30.2%). Preoperative antimicrobials only were administered in 141 of 278 dogs (50.7%), while 45 of 278 dogs (16.2%) only received perioperative antimicrobials. A total of 8 of 278 dogs (2.9%) did not receive pre- or perioperative antimicrobials. Of the dogs that received antimicrobials, ampicillin-sulbactam was administered preoperatively in 204 of 225 (90.7%) and perioperatively in 98 of 133 (73.7%). Enrofloxacin was administered preoperatively in 51 of 225 dogs (22.8%) and perioperatively in 17 of 133 dogs (12.8%). Cefazolin was administered in 24 of 133 dogs (18.0%) perioperatively. Of those that received both pre- and perioperative antimicrobials, the same drug was administered in 58 of 84 (69.0%; ampicillin-sulbactam in all cases). Combination antimicrobial therapy of ampicillin-sulbactam and enrofloxacin was administered preoperatively to 78 of 225 dogs (34.7%).

Culture results

Results of aerobic and anaerobic bacterial cultures of uterine fluid were available for 156 of 278 dogs (56.1%). Results of aerobic bacterial culture only were available in 122 of 278 dogs (43.9%). A total of 276 of 278 cases (99.3%) showed bacterial growth on culture. Bacterial growth was present in 274 of 278 aerobic samples (98.6%) and 13 of 156 samples (8.3%)

submitted for anaerobic bacterial culture. Only 1 isolate was identified in 247 of 278 dogs (88.8%). Two bacterial species were identified in 22 of 278 dogs (7.9%), while 3 and 4 isolates were identified in 4 of 278 (1.4%) and 3 of 278 dogs (1.1%), respectively. No bacterial growth on culture was noted in 2 of 278 dogs (0.7%). Thirty-two distinct bacterial species were identified: 26 of 32 (81.3%) aerobic and 6 of 32 (18.8%) anaerobic. A total of 312 bacterial isolates were identified: 299 of 312 (95.8%) aerobic and 13 of 312 (4.2%) anaerobic. *Escherichia coli* was the most common bacterial isolate (228 of 312 [73.1%]), followed by *Staphylococcus pseudintermedius* (10 of 312 [3.2%]) and β -hemolytic *Streptococcus* (10 of 312 [3.2%]; **Table 3**). Anaerobic isolates included nonspecified *Bacteroides* spp (5 of 312 [1.6%]) and *Bacteroides pyogenes* (3 of 312 [1.0%]), among others.

Histopathology results

Uterine tissue was submitted for histopathology in 29 of 278 dogs (10.4%). Twenty-seven dogs had suppurative endometritis (pyometra) with (19 of 27 [70.3%]) or without (8 of 27 [29.6%]) cystic endometrial hyperplasia. Pyometra was not identified on histopathology in 2 dogs, both of which had positive uterine bacterial culture. Additionally, 2 cases with suspected stump pyometra did not have positive bacterial cultures despite histopathologic changes consistent with pyometra.

Postoperative antimicrobial administration

Of the dogs surviving to discharge, 184 of 272 (67.6%) had 1 antimicrobial agent dispensed for at-home administration. The remaining 88 of 272 dogs (32.4%) were prescribed 2 antimicrobials. Amoxicillin-clavulanic acid was prescribed to 211 of 272 dogs (77.6%) and enrofloxacin was prescribed to 139 of 272 dogs (51.1%). Marbofloxacin was prescribed to 4 of 272 dogs (1.5%) and cefpodoxime was administered to 2 of 272 dogs (0.7%). Ciprofloxacin, doxycycline, metronidazole, and meropenem were each prescribed to 1 of 272 dogs (0.4%). Meropenem was prescribed in response to the results of sensitivity testing available

Table 3—Distribution of bacterial isolates among canines with pyometra.

Bacterial species (N = 312)	No. (%) of total isolates
Aerobic (n = 299)	
<i>Escherichia coli</i>	228 (73.1)
<i>Staphylococcus pseudintermedius</i>	10 (3.2)
β -Hemolytic <i>Streptococcus</i>	10 (3.2)
<i>Streptococcus canis</i>	9 (2.9)
<i>Enterococcus faecalis</i>	8 (2.6)
<i>Proteus mirabilis</i>	7 (2.2)
<i>Haemophilus haemoglobinophilus</i>	6 (1.9)
<i>Enterobacter cloacae</i>	2 (0.6)
<i>Klebsiella oxytoca</i>	2 (0.6)
<i>Klebsiella pneumoniae</i>	2 (0.6)
<i>Klebsiella</i> spp	2 (0.6)
<i>Pseudomonas aeruginosa</i>	2 (0.6)
<i>Actinomyces</i> spp	1 (0.3)
<i>Citrobacter braakii</i>	1 (0.3)
<i>Citrobacter farmeri</i>	1 (0.3)
<i>Enterobacter</i> spp	1 (0.3)
<i>Enterococcus</i> spp	1 (0.3)
<i>Morganella morganii</i>	1 (0.3)
Nonhemolytic <i>Streptococcus</i>	1 (0.3)
<i>Pasteurella canis</i>	1 (0.3)
<i>Serratia marcescens</i>	1 (0.3)
<i>Streptococcus pseudoporcinus</i>	1 (0.3)
<i>Staphylococcus schleiferi</i>	1 (0.3)
Anaerobic (n = 13)	
<i>Bacteroides</i> spp	5 (1.6)
<i>Bacteroides pyogenes</i>	3 (1.0)
<i>Peptostreptococcus</i> spp	2 (0.6)
<i>Bacteroides fragilis</i>	1 (0.3)
<i>Fusobacterium nucleatum</i>	1 (0.3)
<i>Fusobacterium russii</i>	1 (0.3)
<i>Peptoniphilus asaccharolyticus</i>	1 (0.3)

prior to discharge. Median length of postoperative prescriptions was 10 days (range, 4 to 28 days).

Antimicrobial resistance

Median MICs for antimicrobials tested are listed in **Table 4**. Using VET01S edition 4, susceptibility among *E coli* isolates was lowest to cephalaxin (8 of 226 [3.5%]), amoxicillin (41 of 228 [18.0%]), and AMC (69 of 228 [30.3%]). Only 5 of 228 *E coli* isolates (2.2%) were susceptible to all antimicrobials. Resistance to 3 or more antimicrobial classes was seen in 90 of 228 *E coli* isolates (39.5%; **Table 5**). There was significantly lower susceptibility to AMC in NE (21 of 124 [16.9%]) compared to MW (29 of 69 [42.0%]; $P < .001$; OR, 3.56) and CA (19 of 35 [54.3%]; $P < .001$; OR, 5.82) and no difference between MW and CA ($P = .30$). There was no significant difference in susceptibility proportions to enrofloxacin between any of the regions (NE, 120 of 124 [96.8%]; MW, 68 of 69 [98.6%]; CA, 33 of 35 [94.7%]).

Using VET01S edition 7, none of the 228 *E coli* isolates were classified as susceptible to amoxicillin, AMC, cephalaxin, or doxycycline (Table 4).

Compared to VET01S edition 4, application of VET01S edition 7 interpretations resulted in lower susceptibility classifications for 9 of 10 antimicrobials evaluated for *E coli*, with only trimethoprim-sulfamethoxazole showing no change (Table 4). The greatest reductions in susceptibility classification were observed for chloramphenicol (120 of 228 [52.6%]), doxycycline (108 of 228 [47.4%]), AMC (107 of 228 [46.9%]), amoxicillin (95 of 228 [41.7%]),

Table 4—*Escherichia coli* antibiogram in dogs with pyometra.

Drug	Median MIC (μ g/mL)	CLSI VET01S edition	<i>E coli</i> n = 228	<i>E coli</i> (NE) n = 124	<i>E coli</i> (MW) n = 69	<i>E coli</i> (CA) n = 35
AMI	≤ 2	4	226/228 (99.1)	124/124 (100)	68/69 (98.6)	34/35 (97.1)
		7	226/228 (99.1)	124/124 (100)	68/69 (97.1)	35/35 (100)
AMC	2	4	69/228 (30.3)	21/124 (16.9)*†	29/69 (42.0)*	19/35 (54.3)†
		7	0/228 (0)	0/124 (0)	0/69 (0)	0/35 (0)
AMO	4	4	41/228 (18.0)	16/124 (12.9.0)	16/69 (23.2)	9/35 (25.7)
		7	0/228 (0)	0/124 (0)	0/69 (0)	0/35 (0)
CHL	8	4	146/228 (64.0)	74/124 (59.7)	50/69 (72.5)	22/35 (62.9)
		7	27/228 (11.8)	17/124 (13.7)	8/69 (11.6)	2/35 (5.7)
CPD	0.5	4	212/226 (93.8)	113/124 (91.1)	67/69 (97.1)	32/33 (97.0)
		7	211/226 (93.8)	113/124 (91.1)	66/69 (95.7)	32/33 (97.0)
CPL	8	4	8/226 (3.5)	0/124 (0)	5/67 (7.5)	3/35 (8.6)
		7	0/226 (0)	0/124 (0)	0/67 (0)	0/35 (0)
DOX	1	4	212/228 (93.0)	110/124 (88.7)	68/69 (98.6)	34/35 (97.1)
		7	0/228 (0)	0/124 (0)	0/69 (0)	0/35 (0)
ENR	≤ 0.12	4	221/228 (96.9)	120/124 (96.8)	68/69 (98.6)	33/35 (94.7)
		7	215/228 (94.3)	118/124 (95.2)	67/69 (97.1)	30/35 (85.7)
IMI	≤ 0.25	4	227/228 (99.6)	123/124 (99.2)	69/69 (100)	35/35 (100)
		7	226/228 (99.1)	122/124 (98.4)	69/69 (100)	35/35 (100)
TMS	≤ 20	4	220/228 (96.5)	119/124 (96.0)	67/69 (97.1)	34/35 (97.1)
		7	220/228 (96.5)	119/124 (96.0)	67/69 (97.1)	34/35 (97.1)

Data are shown as the proportion (%) susceptible.

AMC = Amoxicillin-clavulanic acid. AMI = Amikacin. AMO = Amoxicillin. CA = California. CHL = Chloramphenicol. CPD = Cefpodoxime. CLSI = Clinical and Laboratory Standards Institute. CPL = Cephalaxin. DOX = Doxycycline. ENR = Enrofloxacin. IMI = Imipenem. MW = Midwest. NE = Northeast. TMS = Trimethoprim-sulfamethoxazole.

* $P < .001$ comparing NE to MW. † $P < .001$ comparing NE to CA.

Table 5—Distribution of antimicrobial susceptibility patterns (ASPs) using CLSI VET01S edition 4 for 228 canine *E coli* isolates by geographic region.

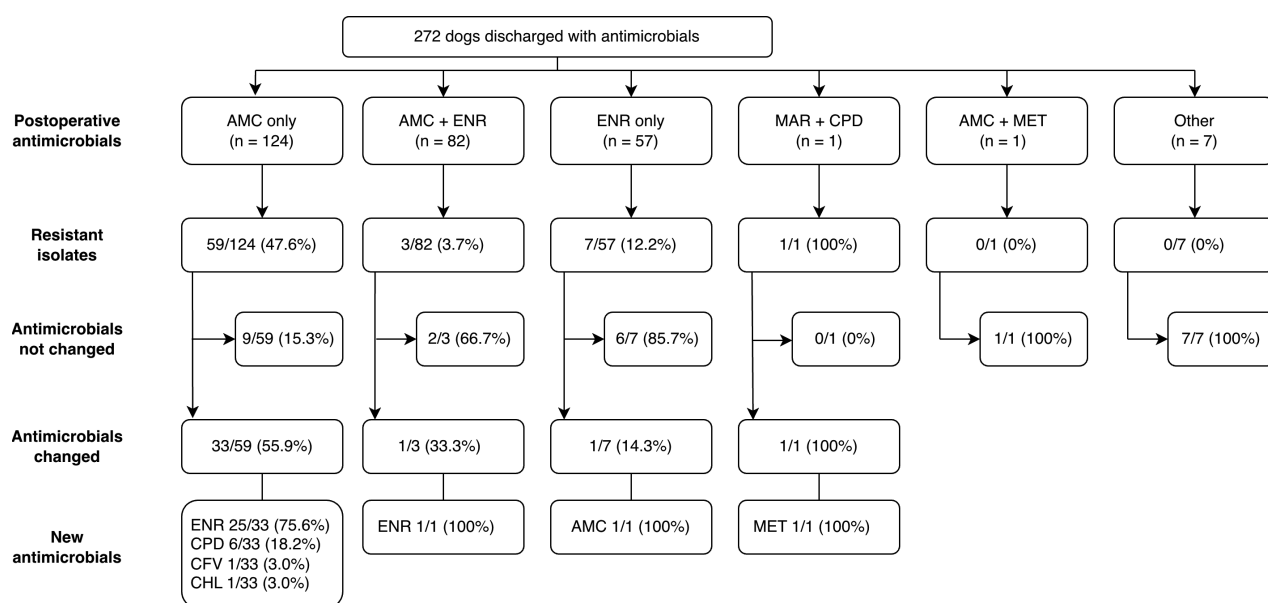
ASP	Prevalence of ASP			
	Total (n = 228)	NE (n = 124)	MW (n = 69)	CA (n = 35)
AMI/CHL/CPD/ENR/IMI/TMS	63 (27.6)	43 (34.7)	17 (24.6)	3 (8.6)
Pansusceptible	48 (21.0)	12 (9.7)	21 (30.4)	15 (42.9)
AMI/CPD/ENR/IMI/TMS	37 (16.2)	31 (25.0)	3 (4.3)	3 (8.6)
AMI/AMC/AMO/CPD/CPL/DOX/ENR/IMI/TMS	20 (8.7)	5 (4.0)	8 (11.6)	7 (20.0)
AMI/AMC/AMO/CHL/CPD/DOX/ENR/IMI/TMS	17 (7.4)	10 (8.1)	4 (5.8)	3 (8.6)
AMI/AMC/AMO/CPD/DOX/ENR/IMI/TMS	6 (2.6)	1 (0.8)	3 (4.3)	2 (5.7)
AMI/ENR/IMI/TMS	5 (2.2)	5 (4.0)	0 (0)	0 (0)
AMI/AMC/CHL/CPD/CPL/DOX/ENR/IMI/TMS	3 (1.3)	1 (0.8)	2 (2.9)	0 (0)
AMI/CHL/ENR/IMI/TMS	3 (1.3)	2 (1.6)	1 (1.4)	0 (0)
AMI/CHL/CPD/CPL/DOX/ENR/IMI/TMS	2 (0.9)	0 (0)	2 (2.9)	0 (0)
AMI/AMC/CPD/CPL/DOX/ENR/IMI/TMS	2 (0.9)	1 (0.8)	1 (1.4)	0 (0)
AMI/AMC/CHL/CPD/ENR/IMI/TMS	2 (0.9)	0 (0)	2 (2.9)	0 (0)
AMI/AMC/CPD/DOX/ENR/IMI/TMS	2 (0.9)	0 (0)	1 (1.4)	0 (0)
AMI/CPD/ENR/IMI	2 (0.9)	2 (1.6)	0 (0)	0 (0)
AMI/CPD/IMI	2 (0.9)	1 (0.8)	0 (0)	1 (2.9)
AMI/AMC/AMO/CHL/CPD/CPL/ENR/IMI/TMS	2 (0.9)	2 (1.6)	0 (0)	0 (0)
AMI/AMC/AMO/CHL/CPD/ENR/IMI/TMS	1 (0.4)	1 (0.8)	0 (0)	0 (0)
AMI/AMC/AMO/CPD/CPL/DOX/ENR/IMI	1 (0.4)	0 (0)	1 (1.4)	0 (0)
AMI/CPD/CPL/DOX/ENR/IMI/TMS	1 (0.4)	0 (0)	1 (1.4)	0 (0)
AMI/AMC/CHL/CPD/CPL/ENR/IMI	1 (0.4)	1 (0.8)	0 (0)	0 (0)
AMI/CHL/DOX/ENR/IMI/TMS	1 (0.4)	1 (0.8)	0 (0)	0 (0)
AMI/CPD/DOX/ENR/IMI/TMS	1 (0.4)	1 (0.8)	0 (0)	0 (0)
AMI/AMC/CHL/DOX/IMI/TMS	1 (0.4)	1 (0.8)	0 (0)	0 (0)
AMI/DOX/ENR/IMI/TMS	1 (0.4)	1 (0.8)	0 (0)	0 (0)
AMI/CHL/CPD/ENR/IMI	1 (0.4)	0 (0)	1 (1.4)	0 (0)
CHL/DOX/IMI/TMS	1 (0.4)	0 (0)	0 (0)	1 (2.9)
AMI/AMC/DOX/IMI	1 (0.4)	1 (0.8)	0 (0)	0 (0)
AMI/IMI/TMS	1 (0.4)	0 (0)	1 (1.4)	0 (0)

Data are shown as number (%).

and cephalexin (78 of 226 [34.5%]). Enrofloxacin (7 of 228 [3.1%]), imipenem (2 of 228 [0.9%]), cefpodoxime (1 of 226 [0.4%]), and amikacin (1 of 228 [0.4%]) showed minimal changes.

In 71 of 272 cases (26.1%), the isolated bacteria were not susceptible to the prescribed postop-

erative antimicrobial under VET01S edition 4 (Table 4). In 36 of 71 dogs (50.7%) with nonsusceptible isolates, the antimicrobial was changed (**Figure 1**). The most common newly prescribed antimicrobials were enrofloxacin in 26 of 36 dogs (72.2%) and cefpodoxime in 7 of 36 dogs (19.4%). Amoxicillin-clavulanic

**Figure 1**—Postoperative antimicrobial administration in 272 dogs with pyometra. AMC = Amoxicillin-clavulanic acid. CFV = Cefovecin. CHL = Chloramphenicol. CPD = Cefpodoxime. ENR = Enrofloxacin. MAR = Marbofloxacin. MET = Metronidazole.

acid, marbofloxacin, chloramphenicol, cefovecin, or metronidazole were each prescribed for 1 of 36 dogs (2.8%). One dog received 3 antimicrobials (marbofloxacin, cefpodoxime, and metronidazole).

Escherichia coli was nonsusceptible to postoperative antimicrobials in 57 of 228 dogs (25.0%), including 40 of 124 (32.2%) in NE, 10 of 69 (14.5%) in MW, and 7 of 35 (20.0%) in CA. With MIC data interpreted using VET01S edition 7, 115 of 272 bacterial isolates (42.3%) would have been classified as nonsusceptible to the prescribed postoperative antimicrobial. Similarly, 102 of 228 *E coli* isolates (44.7%) would have been classified as nonsusceptible to the prescribed postoperative antimicrobials.

Antimicrobial susceptibility patterns

Thirty distinct ASPs were identified among *E coli* isolates using VET01S edition 4. Three susceptibility patterns were present in > 10% of isolates. The most prevalent ASP was amikacin-chloramphenicol-cefpodoxime-doxycycline-enrofloxacin-imipenem-trimethoprim-sulfamethoxazole (74 of 228 [32.5%]; Table 5). Following reinterpretation of the same MIC data using VET01S edition 7 breakpoint criteria, the number of distinct ASPs among *E coli* isolates decreased to 10, with amikacin-cefpodoxime-enrofloxacin-imipenem-trimethoprim-sulfamethoxazole the most common pattern (171 of 228 [75.0%]).

Discussion

To our knowledge, this study was the first to characterize ASPs in canine pyometra in the US. By retrospectively applying standardized CLSI interpretive criteria (VET01S editions 4 and 7) to raw MIC data, this study minimized variability from laboratory-specific susceptibility reporting and evolving breakpoint criteria, allowing comparison of susceptibility patterns across institutions and throughout the study period.

Consistent with prior reports, *E coli* was the predominant bacterial isolate,⁵⁻⁷ with < 40% susceptibility to the commonly prescribed antimicrobials amoxicillin, AMC, and cephalixin. Interestingly, with VET01S edition 4, susceptibility of *E coli* to AMC was lowest in NE, with significantly higher prevalence in MW and CA, while susceptibility to enrofloxacin did not differ significantly between regions. Collectively, these findings highlight both the clinical relevance of AMR in pyometra and the potential influence of geographic factors on susceptibility patterns, underscoring the importance of regionally informed antimicrobial selection.

Clinical and Laboratory Standards Institute VET01S edition 7, published in January 2024, introduced dose-dependent fluoroquinolone breakpoints for Enterobacterales and lowered the resistant breakpoint.²⁵ Forty-eight cases (17.2%) in this cohort underwent surgery after publication of the updated guidelines but had susceptibility interpretations generated with the use of previous criteria. Since previous work has demonstrated inconsistent adherence of veterinary diagnostic laboratories to published antimicrobial susceptibility testing guidelines,²⁷ VET01S edition 4 was used to evaluate historical prescribing since it reflected the criteria available when most treatment decisions were made.

Clinical and Laboratory Standards Institute VET01S edition 7 classifies nonurinary Enterobacterales as uniformly resistant to ampicillin, amoxicillin, and AMC because target tissue concentrations may be insufficient for effective treatment.²⁵ In this cohort, 77.6% of dogs received postoperative AMC and ampicillin-sulbactam was the most common pre- and perioperative antimicrobial. Under current CLSI guidelines, these agents would no longer be considered appropriate empiric therapy for nonurinary *E coli* infections, highlighting the clinical impact of evolving breakpoint interpretations.

Our study population was composed of a representative group of dogs, with signalment, clinical presentation, and clinicopathologic findings consistent with previously reported cases of canine pyometra.⁸⁻¹¹ Common findings included vaginal discharge, neutrophilia, and variable evidence of systemic illness. Survival to discharge was high (97.8%), reflecting the generally favorable prognosis associated with surgical management of this condition.^{7,11,12,21,22}

Antimicrobial administration to hospitalized patients was common in this cohort, with most patients receiving preoperative and nearly half receiving perioperative antimicrobial therapy. Ampicillin-sulbactam was the most frequently administered agent, whereas fluoroquinolones and cephalosporins were used more sparingly. These prescribing patterns are consistent with those reported in both primary care and specialty veterinary settings.^{13,22} Historically, derivatives of amoxicillin have been relied upon in canine pyometra on the basis of high in vitro susceptibility patterns, as well as clinical experience supporting their effectiveness.^{4,5,15} In addition, ampicillin-sulbactam and AMC are components of a broad-spectrum antimicrobial regimen commonly used in cases of suspected or confirmed sepsis, which is a general concern for patients with pyometra.²⁸

Sepsis, defined as SIRS secondary to an infectious insult, may progress to multiple organ dysfunction syndrome and death in severe cases.²⁸ Using the criteria described by Spillane et al,²⁶ 92% of dogs in this study met SIRS criteria; however, these criteria are highly sensitive and poorly specific and may overestimate the true prevalence of clinically significant sepsis. This may explain why only 28.1% of dogs received preoperative combination antimicrobial therapy despite the high proportion meeting SIRS criteria. Additionally, a recently published consensus statement²⁹ on sepsis in dogs and cats recommends using a validated assessment of organ dysfunction for the diagnosis of sepsis instead of SIRS scoring.

Postoperative empirical antimicrobial use was extremely common in this cohort. All dogs except 1 were discharged before culture and susceptibility results were available, and AMC was prescribed most, followed by enrofloxacin. Most dogs were discharged on a single agent; however, some received combination therapy. As a result, the summed percentages reported for individual antimicrobials exceed 100% when combined, reflecting that some patients received more than 1 antimicrobial. The rationale for combination antibiotic therapy in these cases was not recorded but may reflect concern for systemic infection.

In human medicine, empiric combination antimicrobial therapy is often recommended for critically ill patients with suspected sepsis to broaden coverage against anaerobic and MDR pathogens.³⁰ However, evidence supporting improved survival over monotherapy is inconsistent.^{31,32} Likewise, combination therapy in dogs with sepsis was not associated with improved antimicrobial selection or clinical outcome despite similar use of monotherapy and combination therapy (51% vs 49%).²⁸ Together with the increased selection pressure for AMR associated with greater antimicrobial use,¹⁹ these findings support selecting empiric antimicrobials on the basis of accurate susceptibility data rather than unnecessarily broadening coverage.

About 26% of dogs in this study were prescribed an antimicrobial to which the documented infection was nonsusceptible using VET01S edition 4; in most cases, treatment was subsequently switched to enrofloxacin once culture results were obtained. This percentage of patients was lower than the nonsusceptibility rate to AMC, which was observed in over half of the cases in this study. This finding may be attributable to the relatively frequent use of combination antimicrobial therapy, whereby concurrent administration of enrofloxacin often provided effective coverage in cases with resistance to AMC. Evaluation of postoperative antimicrobial prescribing was intentionally performed using VET01S edition 4 because these interpretive criteria most closely reflected the susceptibility information that was available to clinicians during the study period. Consequently, this analysis evaluated prescribing decisions within their historical clinical context.

Bacterial culture results in this study were consistent with the expected pathophysiology of pyometra,^{6,21,33} with nearly all cases yielding growth of single organisms. Aerobic bacteria predominated, while anaerobic isolates were identified in < 10% of dogs, suggesting limited involvement of anaerobic pathogens in the pathophysiology of this condition. *Escherichia coli* was the predominant isolate, with other organisms identified only sporadically, findings that align with previous reports.^{5,6,21,33} Collectively, these findings reinforce empiric therapy targeting aerobic pathogens, particularly *E coli*, in canine pyometra.

Antimicrobial susceptibility for *E coli* was lower than non-*E coli* isolates. Notably, using VET01S edition 4, 39.5% of *E coli* isolates were MDR, defined as nonsusceptible to at least 1 agent in ≥ 3 antimicrobial categories.³⁴ This prevalence is consistent with a previous report³⁵ identifying MDR organisms in canine pyometra. It should be emphasized that interpretation of antimicrobial susceptibility testing for *E coli* has evolved substantially over time, with periodic updates to CLSI breakpoint criteria and laboratory reporting standards. Thus, while an earlier study⁵ reported relatively high susceptibility rates among pyometra isolates, direct comparison of AMR prevalence across historical studies should be interpreted cautiously.

To evaluate the influence of evolving CLSI breakpoint criteria, reflecting increased sensitivity in resistance detection, the same MIC data were reinterpreted using VET01S edition 7. Application

of updated breakpoints resulted in lower susceptibility classifications for 9 of the 10 antimicrobials evaluated, with the greatest reductions observed in chloramphenicol, doxycycline, AMC, amoxicillin, and cephalexin. Likewise, reinterpretation resulted in all *E coli* isolates meeting MDR definition. These findings reinforce the importance of using current CLSI guidelines to reflect evolving pharmacokinetic and pharmacodynamic data.

Antimicrobial resistance remains a major global public health threat,³⁶ with the potential of veterinary patients serving as reservoirs of zoonotic MDR organisms,^{37,38} reinforcing recommendations to restrict veterinary use of critically important antimicrobials.³⁹ A recent genomic study⁴⁰ demonstrated that *E coli* isolates from canine pyometra frequently belong to highly virulent extraintestinal pathogenic lineages, including MDR strains associated with globally disseminated high-risk clones. Mechanisms such as multidrug efflux pumps further confer resistance across multiple antimicrobial classes, increasing the potential for cross-resistance and the development of MDR phenotypes.^{41–43}

Antibiograms provide value in guiding antimicrobial selection by summarizing regional or hospital-specific susceptibility patterns.^{23,44} Using VET01S edition 4 breakpoint criteria, > 80% susceptibility was observed for only 6 of the antimicrobial agents evaluated for *E coli* isolates. Notably, neither AMC (30.3% susceptibility) nor cephalexin (3.5% susceptibility) reached this threshold among *E coli* isolates, suggesting that these agents were unsuitable empiric choices for dogs with pyometra in this cohort.

Considerable variability in ASPs further demonstrated possible regional differences. Thirty distinct ASPs were identified among *E coli* isolates using VET01S edition 4, although only 3 patterns occurred in > 10% of isolates (Table 5). The Northeast showed the greatest diversity of ASPs (19 patterns), followed by MW (13) and CA (11). The most common ASP—susceptibility to amikacin, chloramphenicol, cefpodoxime, doxycycline, enrofloxacin, imipenem, and trimethoprim-sulfamethoxazole—was identified in 74 of 228 isolates (32.5%), with decreasing prevalence from NE to CA. Pansusceptibility was more common in MW and CA compared to NE, further highlighting the geographic variability observed in this study.

Under VET01S edition 4, approximately 30% of *E coli* isolates in NE were susceptible to AMC, a prevalence significantly lower than observed in MW or CA (Table 4). Besides enrofloxacin, the antimicrobial agent with oral formulation showing the highest susceptibility was trimethoprim-sulfamethoxazole, which is the nationally recommended treatment for canine pyometra in Finland.⁴⁵ The inherent nephrotoxicity and risks of hepatic and ocular adverse effects may explain the limited use in this study population and across the US in general,⁴⁶ a particular concern for dogs with acute kidney injury secondary to pyometra. However, a recent study⁴⁶ showed the incidence of these adverse effects to be lower than commonly perceived, with the majority being mild events, suggesting potential utility as a first-line antimicrobial for

susceptible organisms in canine pyometra. While the low prevalence of AMR to enrofloxacin observed in this study may support its use as an empiric antimicrobial option for canine pyometra, fluoroquinolone AMR can develop in as little as 3 days.⁴⁷ Mechanisms of resistance include mutations in the target enzyme's binding site, alterations in cell membrane permeability, and upregulation of efflux pumps.⁴⁷ To minimize further selection pressure toward widespread AMR, empiric fluoroquinolone use without antibiogram guidance should be approached cautiously.

The duration of postoperative antimicrobial administration in this study varied considerably (4 to 28 days), reflecting the lack of consensus regarding appropriate antimicrobial duration following OVH for pyometra. Swedish national guidelines recommend perioperative and postoperative antimicrobial administration only in dogs with moderately to severely depressed mentation or documented sepsis.¹² Additionally, a randomized control trial⁴⁸ identified no difference in the incidence of postoperative urinary tract or incisional infections between dogs with uncomplicated pyometra treated with OVH and either a 5-day course of trimethoprim-sulfamethoxazole or placebo. Collectively, these findings question the necessity of postoperative antimicrobial administration in uncomplicated pyometra cases and, at minimum, support consideration of shorter treatment durations.

Regional variability in AMR of *Staphylococcus* spp and *E coli* has been described for other infectious diseases in companion animals,^{15,17} but not for canine pyometra. Similar regional clustering has been described in human uropathogenic *E coli*, with differences in prescribing practices and environmental factors proposed drivers of resistance.^{20,49} However, because geographic sampling in the present study was limited to a subset of referral hospitals and unevenly distributed across regions, these findings should be interpreted cautiously and may not fully represent broader regional AMR patterns in the US. In human medicine, incorporation of local resistance data into antimicrobial guidelines is recommended.⁵⁰ Collectively, these findings highlight the challenges of empiric antimicrobial selection and support the future prioritization of antibiogram use in veterinary clinical practice.

This study was limited by its retrospective design and variability in medical record availability for all data points. Most dogs received antimicrobials prior to sample collection, which may have contributed to false-negative culture results and further exclusion of eligible cases.

A strength of the present study was the use of raw MIC data, allowing standardized interpretation of antimicrobial susceptibility using a consistent CLSI framework across all laboratories. This minimized variability arising from differing laboratory-utilized breakpoints and evolving CLSI recommendations throughout the study period. Laboratories transition to newly published antimicrobial susceptibility testing interpretation recommendations at varying time points; thus, the specific breakpoint criteria used cannot always be determined retrospectively. This limitation remains when interpreting historical laboratory

reports and susceptibility information available to clinicians. In addition, participating laboratories used different antimicrobial testing panels in the present study, resulting in variable numbers of isolates tested for individual antimicrobial agents. Other aspects of laboratory methodology, including cascade reporting, could also not be standardized retrospectively.

Finally, geographic comparisons in this study should be interpreted cautiously. Case numbers varied among regions because hospitals represented a subset of referral centers within a single veterinary referral network. In addition, regional samples were not evenly distributed among the 3 laboratories performing antimicrobial susceptibility testing, introducing the potential for laboratory-related confounding despite standardized interpretation of MICs. Geographic variability in susceptibility emerged as an unexpected finding, and sampling was not designed to provide equal geographical representation. Although standardized interpretation of MIC data strengthened regional comparisons, additional prospective studies including a broader distribution of hospitals, particularly within the southern US, are needed to determine whether the regional differences identified in this study are representative of the wider canine population.

Overall, the findings of this study demonstrate the high prevalence of AMR in canine pyometra and support the need for continued investigation into the clinical impact of this prevalence on empiric treatment decisions. Future studies should prospectively evaluate antimicrobial use and geographic susceptibility patterns in canine pyometra to optimize treatment strategies. In particular, the need for postoperative antimicrobial use warrants further investigation. When antimicrobial therapy is deemed appropriate, empiric antimicrobial choice should minimize selection for AMR. Furthermore, standardized MIC interpretation is needed to facilitate comparison across institutions and evolving CLSI guidelines. Development of hospital and region-specific veterinary antibiograms would improve empiric antimicrobial selection, facilitate comparison across institutions and regions, and strengthen antimicrobial stewardship. Importantly, the frequent use of AMC observed highlights the importance of translating evolving CLSI breakpoint recommendations into contemporary veterinary prescribing practices through continued clinician education and antimicrobial stewardship efforts.

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