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Antibiograms generated in the United States support use of potentiated sulfonamides and intravenous amoxicillin–clavulanic acid when antimicrobials are needed in *Escherichia coli* canine pyometra

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Objective
Evaluate antimicrobial susceptibility patterns among bacterial pathogens isolated from canine pyometra cases and generate a cumulative antibiogram to inform evidence-based treatment recommendations.

Methods
This observational retrospective study included canine uterine samples submitted for antimicrobial susceptibility testing to Idexx Laboratories and the Cornell University Animal Health Diagnostic Center between 2007 and 2023 in the US. Susceptibility results were interpreted according to current Clinical and Laboratory Standards Institute criteria. Cumulative antibiograms were generated with an interactive app for analysis of diagnostic antimicrobial susceptibility test data (AMR Visualizer; RShiny).

Results
Across the 2 laboratories, 6,462 bacterial isolates were included. *Escherichia coli* was the predominant pathogen (71.7%). Among *E coli* isolates, poor susceptibility was observed to penicillins, β-lactam/β-lactamase inhibitor combinations, tetracyclines, and chloramphenicol. Excellent susceptibility was maintained to aminoglycosides, third-generation cephalosporins, potentiated sulfonamides, and imipenem. Most *E coli* isolates were susceptible-dose-dependent to fluoroquinolones and susceptible with increased exposure to intravenous amoxicillin–clavulanic acid.

Conclusions
Most canine pyometras are caused by *E coli*. The *in vitro* antimicrobial susceptibility patterns of these isolates contribute to understanding resistance trends and support antimicrobial stewardship efforts. Susceptibility should be interpreted in the context of regimens used for breakpoint development.

Clinical Relevance
When perioperative antimicrobial therapy of pyometras is appropriate, veterinarians can use antibiograms to assist in selecting an effective and appropriate antimicrobial before susceptibility test results are available. These antibiograms suggest that folate-pathway inhibitors could be effective empiric choices that align with antimicrobial stewardship principles. High-exposure intravenous amoxicillin–clavulanic acid could be an effective choice in regions where the product is available.

Keywords: pyometra, canine, antimicrobial resistance, antibiogram, *Escherichia coli*

Pyometra is a common and serious bacterial infection of the uterus in intact female dogs, affecting an estimated 20% to 25% of them by middle-aged to older age, with a mean age at diagnosis of approximately 7 years.[1,2] The disease develops during diestrus, when prolonged progesterone exposure induces endometrial proliferation, glandular secretion, and reduced myometrial contractility. This, paired with local immunosuppression, often predisposes dogs to cystic endometrial hyperplasia.[3] These conditions facilitate ascending infection with opportunistic bacteria, most frequently *Escherichia coli*, which in pyometra are

Received May 4, 2026
Accepted August 18, 2026
Published online September 25, 2026

doi.org/10.2460/javma.26.05.0341

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usually distinct from commensal intestinal strains and share virulence traits more commonly with urinary tract pathogens.[4–6] Other organisms, including *Staphylococcus* spp, *Streptococcus* spp, *Pseudomonas* spp, *Proteus* spp, and *Klebsiella* spp, may also be isolated.[2]

Clinical manifestations of pyometra vary widely; common clinical signs include lethargy, dehydration, anorexia, hyporexia, polydipsia and polyuria, fever, and occasionally vomiting.[7] While diagnosis is often straightforward in open-cervix pyometra with vaginal discharge easily noted, closed-cervix cases can present diagnostic challenges and carry a higher risk of systemic illness.[2] Surgical ovariohysterectomy remains the primary definitive treatment for canine pyometra, as it resolves the acute infection and prevents recurrence.[2] The procedure is typically classified as clean-contaminated due to transection of the infected uterus, which could increase the risk for surgical site infection (SSI) and other postoperative complications[8]; however, this classification can vary depending on intraoperative findings and surgeon interpretation.

Antimicrobial therapy is commonly administered perioperatively, yet consensus regarding optimal timing, duration, and agent selection is lacking, and practices vary among clinicans.[7] Retrospective analyses show that antimicrobial regimens are often not aligned with bacterial susceptibility profiles.[4] A survey[8] found that antimicrobial use varied among Arizona-licensed veterinarians; 76% and 74% of clinicians consistently administered antibiotics preoperatively/intraoperatively and postoperatively, respectively, with substantial variability in the choice of drug class and treatment duration. In these cases, only 12% of the respondents regularly submitted a culture.

In 1 Swedish study,[9] all observed SSIs occurred in dogs without pre- or intraoperative antibiotics, while none developed in those that received antibiotics, suggesting a protective effect. In contrast, some authors emphasized a more selective approach, recommending antimicrobial therapy be tailored to clinical severity and infection risk, rather than administered uniformly to all cases.[2,8,9] Additionally, a recent randomized controlled trial[10] demonstrated that placebo was noninferior to postoperative treatment with a folate-pathway inhibitor for SSI prevention when all dogs received a single perioperative antimicrobial dose. Together, these findings suggest that while antimicrobial therapy remains important in the management of canine pyometra, uncertainty persists regarding the most appropriate agents and the timing and duration of treatment. Characterizing susceptibility patterns of pyometra-associated pathogens may contribute to surveillance-level understanding of antimicrobial resistance trends and support the development and refinement of cumulative antibiograms, which in turn may help inform empiric antimicrobial selection and stewardship-guided perioperative treatment protocols.

According to a survey of veterinarians conducted in Arizona, amoxicillin–clavulanate potassium was the most frequently administered antimicrobial agent (86%) for pyometras, followed by enrofloxacin (52%), cefazolin (37%), and ampicillin-sulbactam (22%).[8] Some respondents reported the use of multiple antimicrobial agents, reflecting variability in prescribing practices. International guidelines differ in their recommendations for antimicrobial therapy in canine pyometra. Scandinavian guidelines describe combination antimicrobial therapy primarily in the context of medical (nonsurgical) management, whereas in cases undergoing ovariohysterectomy, antimicrobial use is generally reserved for dogs with moderate to severe systemic illness or sepsis.[7,11–13] Reported drug recommendations across regions vary, with enrofloxacin and amoxicillin-clavulanate used in some guidelines, while others emphasize potentiated folate-pathway inhibitors or ampicillin as alternative options.[7,11–13]

Rising concerns about antimicrobial resistance (AMR) and regional variability in pathogen susceptibility patterns underscore the need for localized evidence-based treatment protocols.[14] Antibiograms are a valuable tool for guiding empiric therapy, tracking changes in AMR, and informing stewardship efforts in veterinary medicine. Antibiograms include organism names, the number of isolates analyzed, the antimicrobial agents tested, and the percentage of each organism interpreted as susceptible to each listed antimicrobial agent based on the standardized clinical breakpoints.[15] Clinical breakpoints are thresholds used to interpret antimicrobial susceptibility test results, translating in vitro MIC values or disk diffusion zones to the in vivo likelihood of therapeutic effectiveness.[16] Isolates classified as susceptible are expected to respond favorably to treatment with the corresponding antimicrobials, whereas isolates categorized as resistant are unlikely to achieve successful clinical outcomes. The objective of this study was to identify predominant canine pyometra pathogens and their resistance profiles, inform empiric perioperative antimicrobial use, support antimicrobial stewardship, and contribute to the broader understanding of resistance trends in canine pyometras.

Methods

Study design and microbiological procedures

Two collections of historic pyometra bacterial culture and susceptibility data were used: isolates from the Cornell University Animal Health Diagnostic Center (AHDC) between 2007 and 2023 and at IDEXX Laboratories between 2018 and 2023. Animal Health Diagnostic Center isolates were primarily from New York state and the northeastern US, whereas IDEXX isolates were submitted from across the US and Canada. At both laboratories, isolates were cultured with standard bacteriological methods for culture and organism identification as previously described.[14,17,18] All AHDC procedures were performed under standardized operating procedures in a laboratory accredited by the American Association of Veterinary Laboratory Diagnosticians, and testing was conducted by IDEXX Laboratories, operated in accordance with international standard ISO/IEC 17025 for laboratory technical competence.

Antimicrobial susceptibility testing of AHDC isolates was performed with the broth microdilution method, as previously described,[17] and interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines **(Table 1)**.

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Table 1—Minimal inhibitory concentration interpretive breakpoints (µg/mL) for classifying *Escherichia coli* isolates as susceptible, intermediate, or resistant.

Antimicrobial	Class	Susceptible	Intermediate	Resistant	Source*
Amikacin	Aminoglycoside	≤ 4	8	≥ 16	Dogs
Amoxicillin–clavulanic acid	Penicillin + β-lactamase inhibitor	≤ 0.25/0.12	0.5/0.25	1/≥ 0.5	Dogs
Ampicillin	Penicillin	≤ 0.25	0.5	≥ 1	Dogs
Cefazolin	Cephalosporin, first and second generation	≤ 2	4	≥ 8	Dogs
Cefpodoxime	Cephalosporin, third and fourth generation	≤ 2	4	≥ 8	Dogs
Ceftazidime	Cephalosporin, third and fourth generation	≤ 4	8	≥ 16	Dogs
Ceftiofur	Cephalosporin, third and fourth generation	≤ 2	4	≥ 8	Swine
Cephalexin	Cephalosporin, first and second generation	≤ 2	4	≥ 8	Dogs
Chloramphenicol	Phenicol	≤ 2	4	≥ 8	Dogs
Doxycycline	Tetracycline	≤ 0.12	0.25	≥ 0.5	Dogs
Enrofloxacin	Fluoroquinolones	≤ 0.6	†0.12–0.25	≥ 0.5	Dogs
Gentamicin	Aminoglycoside	≤ 2	4	≥ 8	Dogs
Imipenem	Carbapenems	≤ 1	2	≥ 4	Humans
Marbofloxacin	Fluoroquinolones	≤ 0.12	†0.25	> 0.5	Dogs
Oribfloxacin	Fluoroquinolones	≤ 1	2-4	≥ 8	Dogs
Piperacillin-tazobactam	Penicillin + β-lactamase inhibitor	≤ 8/4	16/4	≥ 32/4	Dogs
Pradofloxacin	Fluoroquinolones	≤ 0.25	0.5–1	≥ 2	Dogs
Tetracycline	Tetracyclines	≤ 4	6	≥ 16	Humans
Trimethoprim-sulfamethoxazole	Folate pathway antagonists	≤ 2/38	N/A	≥ 4/76	Humans

CLSI = Clinical and Laboratory Standards Institute.

*Section within reference 19 (Clinical and Laboratory Standards Institute. *CLSI VET01S*: *Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals*. Vol 44. 7th ed. Clinical and Laboratory Standards Institute; 2024.). †Susceptible-dose-dependent: clinical efficacy may be achieved if the dosing regimen is optimized (eg, higher dose or increased frequency) according to CLSI breakpoints.[16]

Between 2007 and 2016, Thermo Scientific Sensititre MIC susceptibility plates (COMPAN1F and COMPAN2F panels) were used; after 2016, the COMPGN1F panel was adopted. All MICs were reinterpreted according to the most current CLSI guidelines.[19] Samples processed by IDEXX between 2018 and 2023 were subjected to comparable microbiological culture methods based on client submissions specifying the sampling site and clinical history (uterine and pyometra cases). Antimicrobial susceptibility testing at IDEXX was conducted with the VITEK 2 automated system (bioMérieux) via the VITEK 2 GN-98 card for gram-negative isolates and GP-81 or GP-82 cards for gram-positive isolates[20] in accordance with manufacturer instructions, and MICs were interpreted with current CLSI breakpoints.[19]

Statistical analysis

Preprocessing data—Minimal inhibitory concentrations for microbes from canine uterine isolates (source codes *Ute*, *Utef*, *Utes*, and *Utub* for AHDC data and *Uterus* and *pyometra* for IDEXX data), ranging 16 years from 2007 to 2023 for AHDC data and ranging 5 years from 2018 to 2023 for IDEXX data, were examined. All data preprocessing was performed with statistical software.[21] The AHDC data contained 264 unique samples (ie, uniquely identified by accession, year, patient, and specimen) and 351 unique isolates (ie, uniquely identified by accession, year, patient, specimen, and isolate). In cases where samples contained multiple isolates of the same organism, we examined data from these organisms to determine whether the data likely originated from testing the same isolate across multiple Sensititre panels and therefore could be combined, or whether the data originated from 2 distinct isolates. If the isolates were tested against the exact same panel of drugs and/or they shared at least 1 drug for which the MIC value was incompatible (eg, an MIC of 0.25 and an MIC of > 2 for the same drug), they were determined to represent 2 distinct isolates and be ineligible for data combination. There were no isolates found that were eligible for data combination, so for each sample, only 1 isolate/organism was retained. After this deduplication process, there were 314 unique isolates. The IDEXX data were deduplicated such that each year contained only unique patients and each sample contained unique organisms (the data combination logic described for the AHDC was not applicable to the IDEXX data due to differing data formats). There were 5,666 samples (identified by patient ID, year, and month) and 6,147 isolates (identified by patient ID, year, month, and organism).

MIC interpretation—Minimal inhibitory concentration values were then interpreted based on CLSI breakpoints[19] (Table 1). To align drug and organism names between the data and the interpretative criteria, names were standardized via the AMR package[22] for R and by manual inspection for cases in which the AMR package was incorrect or uncertain. The interpretive criteria were filtered to exclude urinary breakpoints. Interpretation followed a hierarchical approach that first attempted to apply canine-specific breakpoints at the most detailed taxonomic level of bacterial identification (genus and species), then broadened to genus-level canine breakpoints and, where applicable, to order-level canine breakpoints for select bacterial orders (Enterobacterales, Pasteurellaceae, and Pseudomonadales). When canine-specific breakpoints were not available, the interpretation was extrapolated from feline breakpoints, following the same progression from species- to genus- to order-level matching. As a final resort,

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if no canine or feline breakpoints were available, the interpretation was extrapolated from human clinical breakpoints, again following the taxonomic hierarchy from specific to broader classifications. This structured approach ensured the use of the most species-appropriate and taxonomically relevant breakpoints while providing a systematic method for handling cases in which ideal species-specific criteria were unavailable. To verify that correct interpretations were applied, summary tables were made for each organism, displaying the frequency distribution of MIC values within each interpretative category (**Supplementary Table S1** [organism-level summary charts for additional organisms were omitted for brevity, with 2 representative summaries shown]). The proportion of MICs that could not be interpreted were tabulated for each dataset and organism, and any organism-antimicrobial combinations with more than 30% of isolates uninterpretable were excluded from the antibiogram analysis.

Finally, the proportion of possible susceptible-dose-dependent (SDD) isolates and those that were susceptible with increased exposure was calculated when applicable. Initial interpretation of MIC values was performed using S/I/R categories (ie, susceptible, intermediate / increased exposure / resistant) based on CLSI breakpoints and did not include the SDD category. For certain organism-drug combinations, particularly enrofloxacin and marbofloxacin, this resulted in a substantial proportion of isolates being classified as not interpretable. To investigate this, a post hoc analysis was conducted to examine the distribution of MIC values among noninterpretable isolates. For fluoroquinolones with defined SDD breakpoints, isolates with MIC values ≤ 0.25 µg/mL were evaluated as falling within a range that includes CLSI-defined SDD breakpoints. Because MIC values were reported in interval-censored format (eg, ≤ 0.12 µg/mL, ≤ 0.25 µg/mL), isolates within this range could not be definitively classified as either susceptible or SDD. Therefore, SDD was not assigned as a categorical interpretation but was used descriptively to assess the underlying distribution of MIC values contributing to noninterpretable results. The European Union Committee on Antimicrobial Susceptibility Testing (EUCAST)–proposed "susceptible, increased exposure" interpretation was applied to amoxicillin–clavulanic acid for descriptive purposes but was not incorporated into the antibiograms.[23]

AMR Visualizer—Following preprocessing, datasets were uploaded to an interactive app for analysis of diagnostic antimicrobial susceptibility test data (AMR Visualizer; RShiny).[24] Data were imported by selecting the "Import" tab in the left panel and uploading comma-separated value files using the "Browse" function. Upon upload, the dashboard performed additional formatting to ensure compatibility with reporting outputs. Datasets were structured in long format, with each antimicrobial susceptibility result in a separate row; thus, results from a single isolate were spread across multiple rows. During the import process, the dashboard provided previews of both raw and formatted datasets, which were downloaded and inspected for accuracy. The total number of isolates per laboratory and organism frequency was extracted from the "Overview," "Summary Stats," and "Frequency Plot." Antibiograms were generated under the "Antibiogram" tab via filters for the date range of January 1, 2007, to January 1, 2023, and controlled for a maximum of 15 rows. Organism-antimicrobial combinations with fewer than 30 isolates were excluded from **Figures 1 and 2** and included within **Supplementary Materials S1 and S2**. Antibiogram cells were colored based on susceptibility to facilitate visual interpretation of susceptibility patterns as follows: excellent (high susceptibility, teal box highlight), > 90%; moderate (intermediate susceptibility, yellow box highlight), 70% to 90%; and poor (low susceptibility, red box highlight), < 70%. These categories were used for descriptive purposes only and do not represent CLSI-defined susceptibility classifications. The finalized antibiogram report was saved with the "Save Report" function, displaying the prevalence of susceptibility with 95% Clopper-Pearson CIs and the number of isolates tested. Percent susceptibility values displayed in the antibiograms are rounded to the nearest whole number; consequently, when sample sizes are large, zero percent susceptibility may in fact represent values of < 0.5% rather than being exactly zero. This procedure was performed separately for the AHDC and IDEXX datasets. Subsequently, an antibiogram was created for the most common pathogen in each dataset (*E coli*).

MIC percentiles—Minimal inhibitory concentration distributions were computed with the app. Minimal inhibitory concentration values were recorded as character

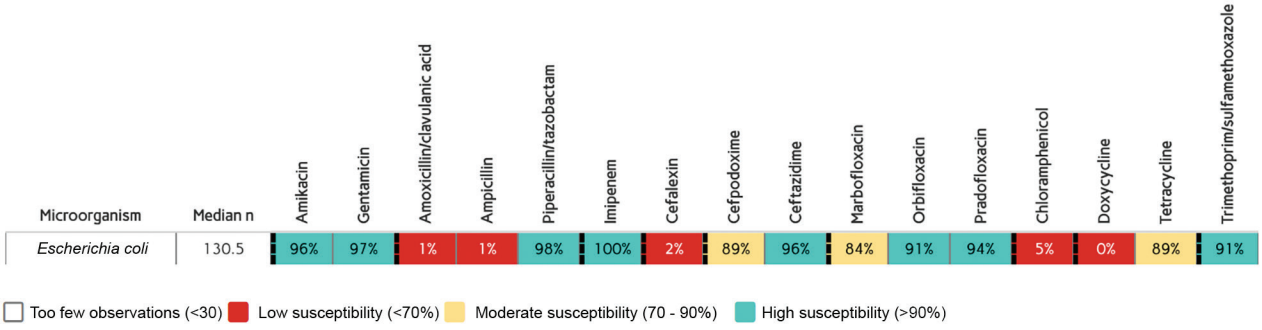

Figure 1—Antibiogram for *Escherichia coli* isolated from canine pyometra submitted to the Animal Health Diagnostic Center between 2007 and 2023.

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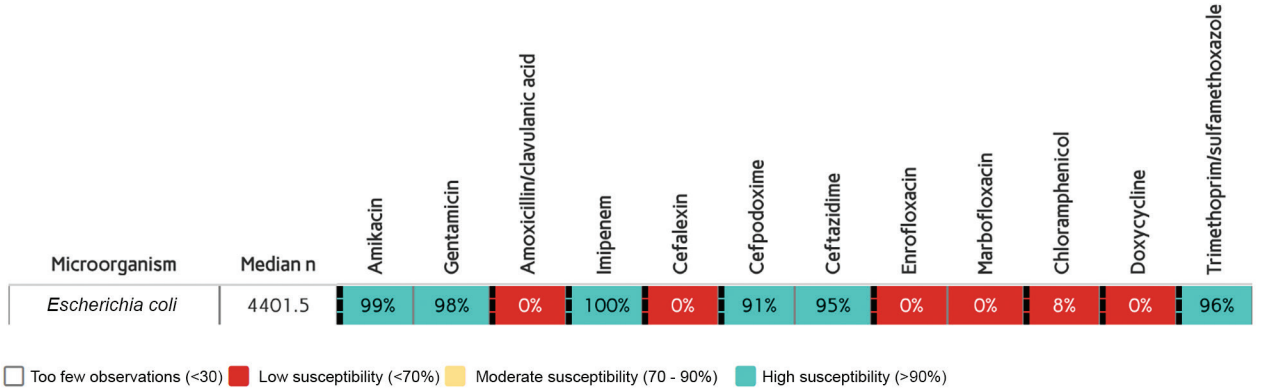

Figure 2—Antibiogram for *E coli* isolated from canine pyometra submitted to Idexx Laboratories Inc between 2018 and 2023.

strings that could include inequality operators (eg, "≤ 0.5", "> 16", "= 1"). To ensure proper ordering of MIC values in the presence of inequality operators, the app parsed each MIC string into an operator component and a numeric value. An ordinal ranking system was established by assigning small offset values (± 0.0001 to ± 0.0002) to the numeric MIC based on the inequality operator. Specifically, "<" values were assigned the smallest offset (−0.0002), followed by "≤" (−0.0001), "=" (0), "≥" (+0.0001), and ">" (+0.0002). This approach preserved the intuitive ordering where, for example, "< 1" < "≤ 1" < "= 1" < "≥ 1" < "> 1" while maintaining the ability to group and count isolates by their original MIC string representation.

For each antimicrobial agent, isolates were grouped by their MIC value and counted. The cumulative distribution was then calculated by ordering MIC values according to the ranking system described earlier and computing the cumulative proportion of isolates at each MIC threshold. The lowest MIC value at which the cumulative proportion of isolates reached or exceeded 50% was defined as MIC_{50}, and the lowest MIC value at which the cumulative proportion reached or exceeded 90% was defined as MIC_{90}. These metrics represented the MIC required to inhibit 50% and 90% of the tested isolates, respectively.

Results

Escherichia coli was the predominant organism isolated in both datasets, accounting for 54.8% (172 of 314) of isolates in the AHDC dataset and 72.5% (4,461 of 6,147) in the IDEXX dataset. In the AHDC dataset, additional organisms with fewer than 30 isolates included *Streptococcus* spp, *Staphylococcus* spp, *Enterococcus* spp, and a variety of other gram-positive and gram-negative organisms tested against their respective antimicrobial susceptibility testing panels (Supplementary Material S1). Within the IDEXX dataset (Supplementary Material S2), other pathogens included *Staphylococcus pseudintermedius* (n = 368), *Enterococcus faecalis* (239), *Proteus mirabilis* (237), *Pseudomonas aeruginosa* (158), *Klebsiella* spp (208), and *Enterobacter* spp (88). Clinical and Laboratory Standards Institute logic rules were not applied in the supplementary antibiogram (eg, *Staphylococcus* β-lactam interpretations were not modified according to oxacillin and penicillin susceptibility, and thus the susceptibility prevalence for other β-lactams should not be interpreted for clinical relevance).

The AHDC *E coli* antibiogram (Figure 1; Supplementary Material S1) demonstrated excellent susceptibility to aminoglycosides (amikacin, 96% [95% CI, 92% to 99%]; gentamicin, 97% [95% CI, 93% to 99%]), the β-lactam/β-lactamase inhibitor combination piperacillin-tazobactam (98%), third-generation cephalosporins (eg, ceftazidime, 96% [95% CI, 91% to 99%]), fluoroquinolones (orbifloxacin, 92% [95% CI, 85% to 96%]; pradofloxacin, 94% [95% CI, 87% to 97%]), potentiated sulfonamides (trimethoprim-sulfamethoxazole, 91% [95% CI, 86% to 95%]), and imipenem (100% [95% CI, 98% to 100%]). Moderate susceptibility was observed for cefpodoxime (89% [95% CI, 84% to 94%]), marbofloxacin (84% [95% CI, 76% to 90%]), and tetracycline (89% [95% CI, 82% to 94%]). Poor susceptibility was observed for amoxicillin–clavulanic acid (1% [95% CI, 0% to 3%]), ampicillin (1% [95% CI, 0% to 3%]), the first-generation cephalosporin cephalexin (2% [95% CI, 0% to 6%]), chloramphenicol (5% [95% CI, 2% to 10%]), and doxycycline (0% [95% CI, 0% to 3%]). Many enrofloxacin and marbofloxacin MICs cross the susceptible and SDD categories, making them not interpretable as a single category. So, although no *E coli* isolates could be definitively classified as susceptible to enrofloxacin, a post hoc analysis of noninterpretable isolates showed that 84% (145 of 172 isolates) had MIC values that encompassed susceptible and SDD interpretive categories for enrofloxacin. Similarly, 88% (152 of 172 isolates) had MIC values that encompassed susceptible and SDD interpretive categories for marbofloxacin. When interpreted with the EUCAST breakpoints, 98% of AHDC *E coli* were susceptible with increased exposure to intravenous amoxicillin–clavulanic acid.

The IDEXX *E coli* antibiogram (Figure 2; Supplementary Material S2) demonstrated excellent susceptibility of *E coli* to aminoglycosides (amikacin, 99% [95% CI, 99% to 99%]; gentamicin, 98% [95% CI, 98% to 98%]); imipenem (100% [95% CI, 99% to 100%]); third-generation cephalosporins, including cefpodoxime (91% [95% CI, 90% to 92%]) and ceftazidime (95% [95% CI, 95% to 96%]); and trimethoprim sulfamethoxazole

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Table 2—Lowest MIC value at which the cumulative proportion of isolates reached or exceeded 50% (MIC_{50}) and lowest MIC value at which the cumulative proportion of isolates reached or exceeded 90% (MIC_{90}) for *E coli* for Idexx and Cornell University Animal Health Diagnostic Center datasets.

	Idexx		AHDC	
Antimicrobial	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**
Amikacin	≤ 2	≤ 2	≤ 4	≤ 4
Amoxicillin–clavulanic acid	2	16	4	8
Ampicillin	NA	NA	2	> 8
Cefalexin	8	16	8	16
Cefpodoxime	≤ 0.25	2	≤ 1	8
Ceftazidime	≤ 0.12	0.5	≤ 4	≤ 4
Chloramphenicol	8	16	8	8
Doxycycline	1	2	≤ 2	8
Enrofloxacin	≤ 0.12	0.5	≤ 0.12	≤ 0.5
Gentamicin	≤ 1	≤ 1	≤ 1	1
Imipenem	≤ 0.25	≤ 0.25	≤ 1	≤ 1
Marbofloxacin	≤ 0.5	≤ 0.5	≤ 0.12	0.5
Orbifloxacin	NA	NA	≤ 1	2
Piperacillin-tazobactam	NA	NA	≤ 8	≤ 8
Pradofloxacin	NA	NA	≤ 0.25	≤ 0.25
Tetracycline	NA	NA	≤ 4	> 8
Trimethoprim-sulfamethoxazole	≤ 1	≤ 1	≤ 0.5	1

NA = Data were not available for that particular antimicrobial.

(96% [95% CI, 95% to 96%]). Poor susceptibility was observed for amoxicillin–clavulanic acid (0% [95% CI, 0% to 0%]), cephalexin (0% [95% CI, 0% to 0%]), chloramphenicol (8% [95% CI, 7% to 9%]), and doxycycline (0% [95% CI, 0% to 0%]). Combined susceptible and SDD prevalence for enrofloxacin was 94% (4,201 of 4,458 isolates) and for marbofloxacin was 90% (3,995 of 4,457 isolates). When amoxicillin–clavulanic acid is used IV, 90% of *E coli* isolates were susceptible with increased exposure based on the EUCAST breakpoint.

Values for MIC_{50} and MIC_{90} in *E coli* isolates are presented in **Table 2**. For many antimicrobials, MIC distributions were broadly similar between the AHDC and IDEXX datasets. These values provide additional context for the categorical susceptibility results presented in Figures 1 and 2.

Discussion

Comparison of AHDC and IDEXX antibiograms revealed broadly consistent susceptibility and resistance patterns for *E coli* despite substantial differences in sample size, the breadth of antimicrobial panels tested, geographic locations, and time periods included. Both datasets demonstrated that *E coli* isolated from pyometras were highly susceptible to aminoglycosides, third-generation cephalosporins, trimethoprim-sulfamethoxazole, and fluoroquinolones (when susceptible and SDD are combined), supporting these antimicrobials as potential empiric therapeutic options when perioperative antimicrobial treatment is clinically warranted. Imipenem demonstrated high susceptibility against most isolates. However, carbapenems are critically important antimicrobials that should be reserved for selected multidrug-resistant infections; therefore, despite favorable in vitro susceptibility, imipenem would not be an appropriate choice for routine empiric perioperative therapy, and in some regions carbapenems may be illegal to use in a companion animal.[25]

The MIC_{50} and MIC_{90} values (Table 2) further characterized the distribution of MIC values within the AHDC and IDEXX *E coli* populations. Several antimicrobials, including amikacin, gentamicin, imipenem, and trimethoprim-sulfamethoxazole, exhibited similar MIC_{50} and MIC_{90} values across both datasets despite differences in laboratory methods, sample size, and geographic representation. Some potential differences in MIC distributions were observed for some antimicrobials, including amoxicillin–clavulanic acid, cefpodoxime, doxycycline, and chloramphenicol, but these observations should be interpreted cautiously because formal statistical comparisons were not performed. Potential explanations included differences in testing platforms, source populations, referral-hospital versus community case mix, geographic sampling, and the substantially smaller sample size of the AHDC dataset as well as inherent variability in susceptibility testing, particularly when breakpoints are set in the wild-type population (eg, amoxicillin–clavulanic acid).[23,26]

Recent CLSI guidelines introduced the SDD category, indicating that clinical efficacy may be achieved when higher antimicrobial exposures are used (eg, higher dose and/or frequency). Importantly, SDD designations are established only for specific organism-drug combinations where pharmacokinetic/pharmacodynamic (PK/PD) and clinical data are available and are not currently defined by CLSI for many antimicrobial agents. The SDD category is established using PK/PD modeling, demonstrating that these dosing regimens can reach therapeutic targets at the defined MIC while remaining safe according to available literature or manufacturer data. It also accounts for minor variability in susceptibility testing, helping prevent small technical differences from significantly altering interpretation.[19] Updated CLSI canine susceptible and SDD breakpoints for enrofloxacin and Enterobacterales (Table 1; susceptible, ≤ 0.06 µg/mL; SDD, 0.12 to

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0.25 µg/mL) are not fully reflected in the current companion gram-negative sensitivity panel (COMPGN1F plate; enrofloxacin MIC range, 0.12 to 4 µg/mL[27]). Consequently, all enrofloxacin MICs of ≤ 0.12 µg/mL and ≤ 0.25 µg/mL measured on the COMPGN1F plates are not interpretable as exclusively susceptible or SDD under updated CLSI breakpoints, which can lead to underestimation of the prevalence of enrofloxacin susceptibility. Therefore, we performed a post hoc analysis of noninterpretable MIC values and found that most fell below the SDD breakpoint but may fall within the SDD or susceptible categories, suggesting that fluoroquinolones may be appropriate for empiric treatment of pyometra; however, isolates categorized as SDD require dose adjustment according to current CLSI recommendations. Current CLSI veterinary guidance indicates MIC-dependent regimens for SDD *E coli* isolates in dogs (for respiratory, skin, and soft tissue and urinary sites), with 10 mg/kg of enrofloxacin orally every 24 hours associated with SDD at an MIC of 0.12 µg/mL and 20 mg/kg orally every 24 hours for SDD at an MIC of 0.25 µg/mL. Similarly, marbofloxacin dosing recommendations vary according to MIC within the SDD range (eg, 5.5 mg/kg orally every 24 hours for higher MIC targets).[19]

Low susceptibility to amoxicillin–clavulanic acid reflects interpretation using current CLSI clinical breakpoints, which are derived from standardized dosing regimens and PK/PD analyses. These breakpoints classify skin and soft tissue canine Enterobacterales infections as resistant when treated with standard oral amoxicillin–clavulanic acid dosing (11 mg/kg of amoxicillin, PO, q 12 h), even when MIC values are small, due to limitations in PK/PD target attainment.[19,28,29] Therefore, the reported low amoxicillin–clavulanic acid susceptibility in this study should not be interpreted as evidence of acquired resistance but rather as a reflection of the PK/PD assumptions underlying the breakpoint criteria used. It suggested that veterinarians should not expect 11 mg/kg of amoxicillin orally to be effective against *E coli* in a pyometra. However, susceptibility interpretations are dependent on the specific dose, formulation, route of administration, and breakpoint criteria applied. The EUCAST has proposed breakpoints for intravenous amoxicillin–clavulanic acid regimens in dogs (20 mg/kg administered over 3 hours or 40 mg/kg administered over 30 minutes q 8 h), although there is not currently a licensed veterinary parenteral amoxicillin–clavulanic acid product in the US or European Union.[23] In the study reported here, over 90% of *E coli* pyometra isolates would be considered susceptible to amoxicillin–clavulanic acid with the increased exposure intravenous dosing regimens. Therefore, intravenous amoxicillin–clavulanic acid could be effective against *E coli* causing pyometras, but veterinarians must pay close attention to the dosing regimen to ensure adequate drug exposure.

Notably, trimethoprim-sulfonamides are recommended as first-line therapy for canine pyometra in some national guidelines due to their high efficacy against *E coli*, with reported susceptibility rates approaching 90% to 95% in both clinical and surveillance datasets (Figures 1 and 2).[30] It should be noted, however, that veterinary-specific clinical breakpoints for folate-pathway inhibitors are currently unavailable and that susceptibility interpretations are extrapolated from human trimethoprim-sulfamethoxazole breakpoints, which could result in different efficacy in dogs than expected based on human susceptibility interpretations.[19,31] In addition to activity against *E coli*, these agents demonstrate efficacy against a broader range of pathogens associated with pyometra, including gram-positive organisms commonly implicated in postoperative infections, although activity against anaerobic organisms may be limited.[10,32] From an antimicrobial stewardship perspective, potentiated sulfonamides are classified as lower-priority agents compared to critically important antimicrobials such as fluoroquinolones, supporting their use as preferable alternatives when clinically appropriate.[32] While sulfonamides have historically been associated with adverse effects in dogs, available clinical data suggest that clinically significant reactions are uncommon. A recent systematic review[33] estimated the prevalence of severe adverse events at 0.2%, and a large VetCompass Australia cohort study[34] reported that keratoconjunctivitis sicca, one of the most frequently cited concerns associated with trimethoprim-sulfonamide administration, was rare in treated dogs. Furthermore, a study evaluating postoperative trimethoprim-sulfadiazine in dogs with pyometra reported that observed adverse events were largely attributable to postoperative physiological responses rather than drug-specific toxicity.[32,33] Collectively, these findings support considering trimethoprim-sulfonamides as an effective, lower-tier empiric option when antimicrobial therapy is clinically indicated in pyometra.[32]

The widespread, often empiric use of postoperative antimicrobial therapy for pyometras in the absence of supporting susceptibility data and clinical indications (eg, sepsis) raises concerns for the selection of AMR.[35–38] In companion animals, this has implications not only for individual patient outcomes but also for population-level resistance dynamics, given the close contact between pets, veterinary staff, and owners.[35–39] Postoperative antimicrobial therapy for pyometra commonly includes amoxicillin–clavulanic acid, ampicillin-sulbactam, and fluoroquinolones.[8,40,41] According to a survey, three-quarters of Arizona veterinarians always prescribed postoperative antibiotics for pyometra, often exceeding 2 weeks of treatment. Culture and susceptibility testing were often not performed due to cost considerations, leading veterinarians to rely on experience to determine which antimicrobial treatment to use and when.[8] Clinical indicators prompting postoperative antimicrobial use among surveyed veterinarians included fever, signs of sepsis, peritonitis, and closed pyometras.[8] However, from an antimicrobial stewardship perspective, routine postoperative antimicrobial therapy following surgical source control in uncomplicated pyometra is likely unnecessary. A recent study[32] in Finland found that postoperative antimicrobial treatment had no effect on rates of SSI or urinary tract infections when uncomplicated canine pyometra

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cases were treated with a single perioperative dose of trimethoprim-sulfadoxine. A Swedish study[9] reported that only 11% of 90 dogs managed without antimicrobial therapy before or during surgery developed infectious complications. In that study, treatment decisions were based on general demeanor before and during surgery, and under Swedish legislation, routine antimicrobial use is discouraged and reserved for life-threatening infections. Furthermore, previous studies[4,42] have demonstrated favorable clinical outcomes even when peri- or postoperative antimicrobial therapy did not align with in vitro susceptibility profiles, including dogs with peritonitis. These findings suggest that successful treatment of canine pyometra is primarily dependent on effective surgical source control, with antimicrobial therapy often playing a secondary role through the combined effects of host immune responses and antimicrobial penetration into infected tissues.[4] When postoperative antimicrobial therapy is clinically indicated, such as in dogs with systemic illness or abdominal cavity contamination, initial empiric antimicrobial selection should be guided by local susceptibility patterns, with culture and susceptibility testing performed whenever feasible to refine therapy once results become available, following antimicrobial stewardship principles.[35–38] Based on the antibiograms presented here, oral amoxicillin–clavulanic acid appears to be a poor empiric choice because of their PK/PD profile with the predominant pyometra pathogen, *E coli* (Figures 1 and 2).[23] Instead, trimethoprim-sulfamethoxazole, intravenous high-dose amoxicillin–clavulanic acid, third-generation cephalosporins, aminoglycosides, or fluoroquinolones are more appropriate empiric options when antimicrobial therapy is clinically indicated.[8,9] Veterinarians should also consider regional or national guidelines and the importance of antimicrobials to human health when selecting an antimicrobial; generally, trimethoprim-sulfamethoxazole and intravenous amoxicillin–clavulanic acid are the most appropriate empiric choices for antimicrobial stewardship when drugs with high susceptibility in these antibiograms are considered.

A key limitation of this study was the potential for sampling bias in antimicrobial susceptibility testing data. Testing may be constrained by cost, time, or clinical urgency; samples are more likely to be submitted following treatment failure rather than at initial presentation. The isolates in the AHDC dataset may reflect cases more commonly managed by specialists rather than general practitioners, given that the Cornell University Hospital for Animals is one of the primary sources of AHDC submissions. The extent of this bias is difficult to quantify due to limited information on the clinical context and rationale for test submission. Disparities between the datasets may also arise from differences in susceptibility testing methods used by the AHDC (microbroth dilution via the Thermo Scientific Sensititre system) and IDEXX (VITEK 2 automated system via bioMérieux). Another potential limitation to our study was that our data were limited to the US and do not reflect international results.

Future prospective studies are needed to further define optimal treatment strategies for canine pyometra, including systematic evaluation of peri- and postoperative antimicrobial use, optimal treatment durations to maximize clinical efficacy while minimizing the risk of AMR, and a comparative assessment of the clinical effectiveness of specific antimicrobial agents. Such studies should integrate clinical outcomes, surgical variables, host factors, and susceptibility data to better delineate when antimicrobial therapy provides meaningful benefit and when it may be safely reduced or omitted. Overall, the antibiograms presented here suggested the judicious use of fluoroquinolones at appropriately high dosages for efficacy against SDD isolates, third-generation cephalosporins, intravenous amoxicillin–clavulanic acid, and trimethoprim-sulfamethoxazole for effective perioperative treatment and, when clinically justified, short-duration postoperative treatment of canine pyometra. As trimethoprim-sulfamethoxazole and related folate-pathway inhibitors are older drugs and not as important for human medicine, we recommend that veterinarians should consider them as a first-line option for pyometras. Studies establishing PK/PD breakpoints specific to dogs for folate-pathway inhibitors would strengthen this recommendation. The susceptibility patterns and treatment considerations presented are based on currently accepted CLSI veterinary breakpoints. While future revisions to breakpoint criteria may alter susceptibility categorizations for some organism-antimicrobial combinations, cumulative antibiograms remain an important tool for guiding empiric antimicrobial selection and supporting antimicrobial stewardship in canine pyometra.

Acknowledgments

The authors would like to thank IDEXX Laboratories for their provision of data and Melissa Aprea for the curation of the Cornell University Animal Health Diagnostic Center antimicrobial resistance data. The data analyzed in this study are subject to the following licenses/restrictions: privately owned commercial dataset. Requests to access these datasets should be directed to IDEXX Laboratories Inc and the Cornell University Animal Health Diagnostic Center. The authors would like to thank the many contributors who helped to develop and improve the AMR Visualizer. A complete list of contributors to the AMR Visualizer can be found at https://github.com/AMR-Visualizer.

Disclosures

Donald Szlosek was employed by IDEXX Laboratories Inc. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Dr. Cazer is a member of the *JAVMA* Scientific Review Board. She was not involved in the editorial evaluation of or decision to accept this article for publication.

Generative AI was not used in the writing of this manuscript. Grammarly and ChatGPT (OpenAI) were used as proofreading and editing tools and were employed only to refine the language and grammar of this document. All scientific interpretations, data analysis, and conclusions were independently developed and verified by the authors.

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Funding

This work was supported in part by USDA APHIS. It does not necessarily represent the views of USDA APHIS.

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Supplementary Materials

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