Article

Antimicrobial resistance trends among canine *Escherichia coli* isolates obtained from clinical samples in the northeastern USA, 2004–2011

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Abstract — Our objectives were to describe the antimicrobial susceptibility of *Escherichia coli* isolates from dogs in the northeastern USA and to identify temporal trends in resistance to selected antimicrobial agents. Data were collected retrospectively for all canine *E. coli* isolates from clinical samples submitted to Cornell University's Animal Health Diagnostic Center between January 1, 2004 and December 31, 2011. Antimicrobial susceptibility testing was performed on 3519 canine *E. coli* isolates; frequency of resistance to each agent ranged from 0.4% (amikacin) to 34.3% (ampicillin). No trends were evident among urinary isolates, but cephalosporin resistance remained consistently high. Among non-urinary isolates, there was evidence of a significantly increasing trend in prevalence of resistance to several agents, including cephalosporins, enrofloxacin, and tetracycline. These data suggest that some of the most commonly used antimicrobial agents in companion animal practice are becoming less effective against canine *E. coli* infections outside the urinary tract.

Résumé — Tendances de la résistance antimicrobienne parmi les isolats canins d'*Escherichia coli* obtenus dans des échantillons cliniques dans le nord-est des États-Unis de 2004 à 2011. Nos objectifs consistaient à décrire la susceptibilité des isolats d'*Escherichia coli* chez des chiens dans le nord-est des États-Unis et à identifier les tendances de résistance temporelles aux agents antimicrobiens sélectionnés. Des données ont été recueillies rétrospectivement pour tous les isolats canins d'*E. coli* provenant d'échantillons cliniques soumis à l'Animal Health Diagnostic Center de l'Université Cornell entre le 1er janvier 2004 et le 31 décembre 2011. Des épreuves de sensibilité antimicrobienne ont été réalisées sur 3519 isolats canins *E. coli;* la fréquence de résistance à chaque agent allait de 0,4 % (amikacine) à 34,3 % (ampicilline). Aucunes tendances n'étaient évidentes parmi les isolats urinaires, mais la résistance à la céphalosporine demeurait constamment élevée. Parmi les isolats non urinaires, il y avait des preuves d'une tendance significative à la hausse de la prévalence de la résistance à plusieurs agents, y compris les céphalosporines, l'enrofloxacine et la tétracycline. Ces données suggèrent que certains des agents antimicrobiens les plus communément utilisés en pratique des animaux de compagnie deviennent de moins en moins efficaces contre les infections canines par *E. coli* à l'extérieur des voies urinaires.

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Introduction

Antimicrobial resistance among bacteria isolated from companion animals is an emerging problem with implications for patient management and public health (1). In dogs, common bacterial infections that are treated with antimicrobial agents include gastroenteritis, otitis, pyoderma, respiratory infections, urinary tract infections (UTIs), and wound infections (2–4). Antimicrobial resistance limits treatment options and increases the risk of therapeutic failure. In addition, the occurrence of drug-resistant bacteria in dogs represents a potential threat to human health. Evidence suggests that direct contact between companion animals and humans can lead to interspecies transmission of pathogenic bacteria, including strains that demonstrate antimicrobial resistance (5,6).

Escherichia coli is a useful sentinel organism for monitoring antimicrobial susceptibility in dogs and other species (4,7). Some strains are commensal organisms in the mammalian intestinal tract, but *E. coli* is also one of the most frequently isolated bacterial pathogens in companion animal practice (8,9). Most recognized mechanisms of antimicrobial resistance have been detected in *E. coli,* and it is an organism that readily acquires resistance in the face of local selection pressure (10,11). Thus, *E. coli* is a key source of antimicrobial resistance genes that could confer resistance to other bacterial pathogens via horizontal transfer mechanisms (1). However, the scope of our

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Table 1. Resistance to individual antimicrobial agents among *E. coli* isolates from dogs in the northeastern USA, 2004–2011

Antimicrobial agent	Number of isolates tested	% Resistant
Ampicillin	3480	34.3
Cephalothin	1325	27.9
Tetracycline	2974	23.6
Cefazolin	1669	22.9
Cefoxitin	1686	19.9
Enrofloxacin	3473	18.1
Trimethoprim/sulfamethoxazole	3474	17.9
Amoxicillin/clavulanic acid	3476	15.7
Gentamicin	1713	15.5
Chloramphenicol	1711	12.6
Amikacin	1711	0.4

understanding has been constrained by limited surveillance for antimicrobial resistance among *E. coli* and other bacteria isolated from companion animals.

The objectives of this study were thus to describe the antimicrobial susceptibility of *E. coli* isolates from dogs in New York and other northeastern states during 2004–2011 and to identify trends in resistance to certain antimicrobial agents over time. This information may help to guide empiric selection of antimicrobial agents when treating canine infections and may serve to further inform the discussion of judicious antimicrobial use in companion animal practice.

Materials and methods

Study design

We collected data retrospectively for all canine *E. coli* isolates that were obtained from clinical samples submitted to the Cornell University Animal Health Diagnostic Center (AHDC) between January 1, 2004 and December 31, 2011 and that were subsequently tested for antimicrobial susceptibility. Based on AHDC canine sample submission data over an overlapping time frame of comparable duration, we estimate that 65% of samples were submitted by regional veterinary practices and 35% by the Cornell University Hospital for Animals (CUHA). The proportion of samples submitted by the CUHA on an annual basis during this time frame ranged from 33% to 39%. We assume that a history of clinical disease generally prompted sample submission by practitioners. Variables collected from the computerized records database included the date of *E. coli* isolation, sample source, and susceptibility to each antimicrobial agent. Information concerning disease severity and previous therapy was not available.

Microbiologic procedure for *E. coli* detection

Personnel at the AHDC used standard bacteriologic culture methods to isolate *E. coli* from samples. Briefly, sample material was inoculated onto Columbia agar with 5% sheep blood and onto Eosin Methylene Blue (EMB) agar. Individual colonies were then chosen as presumptive for *E. coli* based upon morphology. Identity of isolates was confirmed as *E. coli* using the Sensititre Automated Microbiology System (TREK Diagnostic Systems, Cleveland, Ohio, USA). Guidelines established by the Clinical and Laboratory Standards Institute (CLSI) were used throughout the isolation process (12).

Antimicrobial susceptibility testing

Antimicrobial susceptibility of *E. coli* isolates was determined by use of the broth microdilution method. Minimal inhibitory concentrations (MIC) were established for each isolate against various panels of antimicrobial agents. The antimicrobial agents selected for this study have pharmacologic activity against *E. coli* and are clinically relevant to canine medicine, either through therapeutic use or as markers for susceptibility to commonly used agents. This list includes amikacin (AMI), amoxicillin/clavulanic acid (AUG), ampicillin (AMP), cefazolin (FAZ), cefoxitin (FOX), cephalothin (CEP; used as a marker for susceptibility to other first-generation cephalosporins including cephalexin and cefadroxil), chloramphenicol (CHL), enrofloxacin (ENRO), gentamicin (GEN), tetracycline (TET), and trimethoprim/sulfamethoxazole (SXT). The CLSI guidelines were used to interpret MIC values (13,14). Regardless of isolation year, all MIC values were interpreted using the same set of current guidelines. Isolates were classified as being resistant or susceptible to each agent; those few isolates with intermediate susceptibility were categorized as being susceptible. Quality control was performed weekly using *Escherichia coli* ATCC 25922, *Staphylococcus aureus* 29213, *Enterococcus faecalis* 29212, and *Pseudomonas aeruginosa* 27853. The MIC ranges for quality control recommended by the CLSI were used, and results were accepted if the MIC values were within expected ranges for these bacterial strains.

Statistical analysis

Data were imported into a commercial statistical software program (SAS, version 9.2; SAS Institute, Cary, North Carolina, USA) for variable coding and analysis. Descriptive analysis was performed on all variables. Associations between antimicrobial resistance and isolate source were analyzed using separate logistic regression models for each agent, while controlling for year of isolation. Susceptibility status (resistant or not) was used as the dichotomous outcome variable in these models. Temporal trends in the prevalence of resistant *E. coli* between 2004 and 2011 were investigated for each antimicrobial agent using the Cochran-Armitage trend test. For all analyses, P-values < 0.05 were considered significant.

Results

Between January 1, 2004 and December 31, 2011, the AHDC performed antimicrobial susceptibility testing on 3519 canine *E. coli* isolates from submitted clinical samples. Among these isolates, 57.8% (2034) were obtained from urine or urinary tract samples, 7.1% (251) from external ear samples, 4.5% (160) from wounds or other integumentary samples, 3.8% (132) from feces or intestinal tract samples, 2.8% (98) from respiratory tract samples, 22.1% (779) from miscellaneous locations (including blood, bone, cerebrospinal fluid, eye, gall bladder, joint, liver, lymph node, reproductive tract, and spleen), and 1.8% (65) from unspecified locations. Antimicrobial agents were used with varying frequency for MIC determinations, with a median of 1713 isolates (range: 1325 to 3480) being tested for susceptibility to each agent.

Frequency of resistance to individual antimicrobial agents (Table 1) ranged from 0.4% (amikacin) to 34.3% (ampicillin) of all isolates tested. Urinary isolates displayed a higher frequency

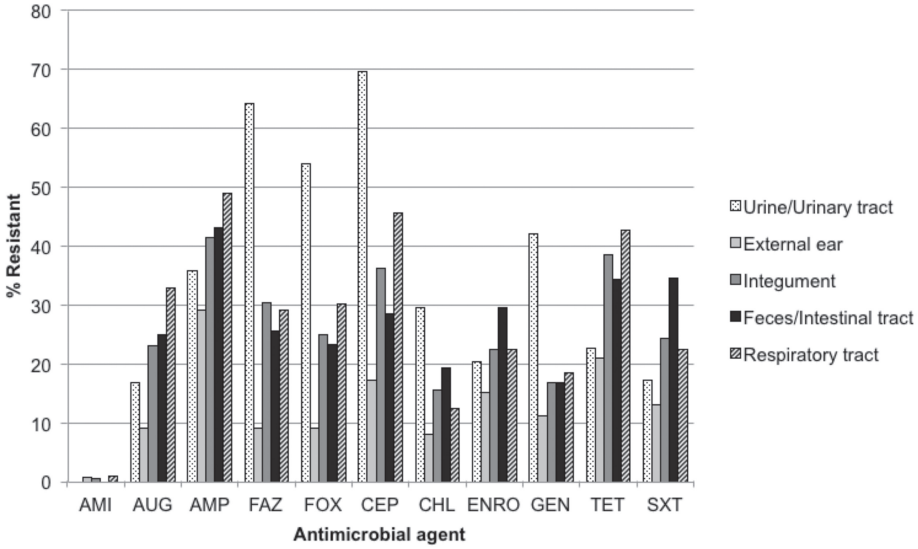

Figure 1. Resistance to individual antimicrobial agents among canine *E. coli* isolates stratified by sample source, 2004–2011.

AMI – amikacin; AUG – amoxicillin/clavulanic acid; AMP – ampicillin; FAZ – cefazolin; FOX – cefoxitin; CEP – cephalothin; CHL – chloramphenicol; ENRO – enrofloxacin; GEN – gentamicin; TET – tetracycline; SXT – trimethoprim/sulfamethoxazole

Table 2. Most common resistance patterns among 1161 canine *E. coli* isolates that were tested for susceptibility to all antimicrobial agents used in this study, 2004–2011

Resistance pattern[a]	Number of isolates	% of isolates
Pan-susceptible	606	52.2
AUG-AMP-FAZ-FOX-CEP-ENRO-GEN-TET-SXT	47	4.0
AMP	45	3.9
AUG-AMP-FAZ-FOX-CEP-CHL-ENRO-GEN-TET-SXT	37	3.2
TET	28	2.4
AUG-AMP-FAZ-FOX-CEP-CHL-ENRO-TET-SXT	25	2.2
AUG-AMP-FAZ-FOX-CEP	21	1.8
AMP-TET-SXT	20	1.7
AMP-ENRO-GEN-TET-SXT	14	1.2
AUG-AMP-FAZ-FOX-CEP-ENRO-TET	13	1.1
AUG-AMP-FAZ-FOX-CEP-ENRO-TET-SXT	11	0.9
AMP-ENRO-TET-SXT	11	0.9

[a] AUG — amoxicillin/clavulanic acid; AMP — ampicillin; FAZ — cefazolin; FOX — cefoxitin; CEP — cephalothin; CHL — chloramphenicol; ENRO — enrofloxacin; GEN — gentamicin; TET — tetracycline; SXT — trimethoprim/sulfamethoxazole.

of resistance to cephalosporins than to any other class of agent (Figure 1), with more than half being resistant to cefazolin (64.3%), cefoxitin (54.1%), and cephalothin (69.7%). In contrast, resistance to ampicillin was most frequent among isolates from the external ear (29.1%), integument (41.5%), intestinal tract (43.1%), and respiratory tract (49.0%; Figure 1). Among the 1161 isolates that were tested using all antimicrobial agents in this study, the most common resistance patterns (Table 2) were pan-susceptible (52.2%), AUG-AMP-FAZ-FOX-CEP-ENRO-GEN-TET-SXT (4.0%), AMP (3.9%), and AUG-AMP-FAZ-FOX-CEP-CHL-ENRO-GEN-TET-SXT (3.2%). Multidrug resistance, defined here as *in vitro* resistance to 2 or more classes of antimicrobial agent, was observed in 38.8% (450/1161) of isolates that were tested using all antimicrobial agents in this study.

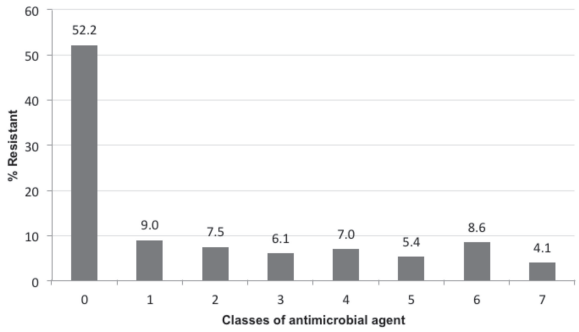

Figure 2. Distribution of resistance by number of antimicrobial classes among 1161 canine *E. coli* isolates that were tested for susceptibility to all antimicrobial agents used in this study, 2004–2011.

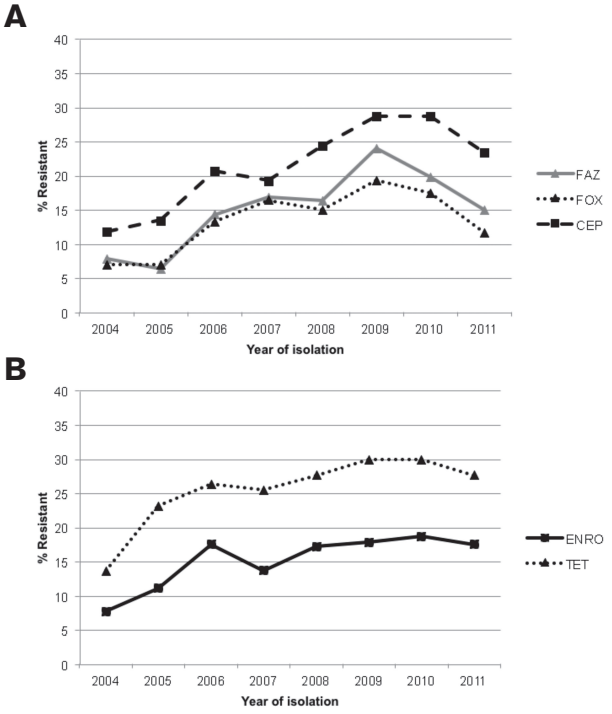

Figure 3. A – Temporal trends in the prevalence of cephalosporin resistance among non-urinary *E. coli* isolates from dogs in the northeastern USA, 2004–2011.
FAZ – cefazolin; FOX – cefoxitin; CEP – cephalothin

B – Temporal trends in the prevalence of enrofloxacin and tetracycline resistance among non-urinary *E. coli* isolates from dogs in the northeastern USA, 2004–2011.
ENRO – enrofloxacin; TET – tetracycline

Resistance to a single class of antimicrobial agent was observed in 9.0% (105/1161) of these isolates (Figure 2).

Multivariable logistic regression analysis showed that urinary isolates were significantly more likely than non-urinary isolates (i.e., isolates from all other specified sources) to demonstrate *in vitro* resistance to cefazolin [odds ratio (OR) = 9.7; 95% confidence interval (95% CI) = 7.1 to 13.2; $P < 0.0001$], cefoxitin (OR = 7.1; 95% CI = 5.2 to 9.5; $P < 0.0001$), cephalothin (OR = 8.9; 95% CI = 6.3 to 12.5; $P < 0.0001$), chloramphenicol (OR = 4.2; 95% CI = 3.0 to 5.9; $P < 0.0001$), and gentamicin (OR = 5.9; 95% CI = 4.3 to 8.0; $P < 0.0001$), after accounting for year of isolation. Resistance to other antimicrobial agents did not differ significantly by isolate source. Among the isolates that were tested using all antimicrobial agents in this study, urinary isolates were significantly more likely to be multidrug-resistant than were non-urinary isolates (OR = 11.4; 95% CI = 7.4 to 17.6; $P < 0.0001$), after accounting for year of isolation.

The Cochran-Armitage test revealed no significant temporal trends for antimicrobial resistance among urinary isolates. In contrast, among non-urinary isolates there was evidence of a significantly increasing trend in prevalence of resistance to several antimicrobial agents over time: cefazolin ($P = 0.0002$), cefoxitin ($P = 0.02$), cephalothin ($P = 0.0003$), enrofloxacin ($P = 0.04$), and tetracycline ($P = 0.0007$) (Figures 3A, 3B). There were no significant trends for resistance to amikacin, amoxicillin/clavulanic acid, ampicillin, chloramphenicol, gentamicin, or trimethoprim/sulfamethoxazole among non-urinary isolates.

Discussion

Monitoring antimicrobial resistance trends among bacteria isolated from dogs is useful for guiding antimicrobial use practices in companion animal medicine. Although antimicrobial susceptibility among bacteria isolated from food animals is regularly monitored through various federal programs (15,16), targeted surveillance in companion animals has been limited. This study was based on data collected from the AHDC database over an 8-year period, including 3519 clinical canine *E. coli* isolates which had been subjected to antimicrobial susceptibility testing. Although not all isolates were tested for susceptibility to each of the 11 antimicrobial agents used in this study, the scope of our sample (in terms of isolate number and time span) and source of our isolates (diagnostic laboratory submissions from a single geographic region) made this a valuable dataset for studying antimicrobial resistance trends.

Escherichia coli was isolated from a diverse array of body sites during the study period, but the predominant source of isolates was the urinary tract. This is in agreement with other studies in which the urinary tract was the most common source of clinical canine *E. coli* isolates (4,17). Urinary tract infections are observed frequently in dogs, especially older female dogs, and are generally caused by ascending bacteria (18,19). Clinical signs can include stranguria, pollakiuria, and hematuria (9). Canine UTIs are typically uncomplicated and resolve with an appropriate course of oral antimicrobial therapy (20). However, infections can be persistent or recurrent because of pathogen factors or predisposing conditions in the host (21,22). *Escherichia coli* is the most common pathogen isolated from the canine urinary tract, accounting for 40% to 50% of isolates from clinical cases of UTI (18,21–25).

Urinary *E. coli* isolates were more likely to be multidrug-resistant than were isolates from other body sites, after accounting for year of isolation. Cephalosporins had the poorest *in vitro* efficacy against urinary isolates, with resistance frequency ranging from 54% to 70% depending on the agent. Selection pressure associated with prior antimicrobial therapy may be responsible for the relatively high resistance to cephalosporins among urinary isolates in this study. A number of samples, particularly among those submitted by CUHA veterinarians, likely originated from dogs that had received previous antimicrobial therapy, and cephalosporins are commonly recommended for treating canine UTIs (20). Cephalosporins are excreted by the kidneys, and recent work highlights the potential of their metabolites to exert selection pressure for resistant *E. coli* (26). Alternatively, cephalosporin resistance genes could be physically linked to virulence genes that facilitate colonization and infection of the urinary tract. Various beta-lactamase genes, which are the most important mediators of cephalosporin resistance in *E. coli,* are increasingly being recognized among uropathogenic and other extraintestinal pathogenic *E. coli* (27). A number of *E. coli* sequence types, including the uropathogenic ST131, appear to be experiencing clonal expansion as a result of a combination of antimicrobial resistance [including resistance

conferred by extended-spectrum beta-lactamases (ESBL)] and assorted virulence mechanisms (28–31).

Among canine non-urinary *E. coli* isolates, the prevalence of resistance to several antimicrobial agents, including cefazolin, cefoxitin, cephalothin, enrofloxacin, and tetracycline, increased significantly over the 2004–2011 study period. Interestingly, these increasing trends in resistance were not evident among urinary *E. coli* isolates; cephalosporin resistance remained consistently high among these isolates during the study period. Furthermore, there were no decreasing trends in resistance to any of the agents in this study, regardless of isolate source. These results suggest that current antimicrobial use practices in canine medicine might be driving an increase in the emergence and dissemination of drug-resistant *E. coli* in the region served by the laboratory. The scope of our conclusions is limited by our lack of antimicrobial use data from this population of dogs during the time frame of interest. However, cephalosporins, enrofloxacin, and doxycycline were recently found to be among the most commonly prescribed antimicrobial agents at a small animal teaching hospital in the northeastern United States (3). Regardless of the cause, our data suggest that some of the most commonly used agents in companion animal practice are becoming less effective against canine *E. coli* infections outside the urinary tract. Our data also suggest that cephalosporins are not likely to be effective against the relatively high percentage of canine UTIs that are caused by *E. coli.* It is important to note, however, that resistance to antimicrobial agents of the beta-lactam class among *E. coli* isolates in the urinary tract does not necessarily presage treatment failures of those agents at that anatomic site. Resistance is defined by the concentration of antimicrobial agent achievable in the serum. As this class of agents is concentrated highly in urine, they may reach concentrations sufficient to overcome the high resistance levels that we observed and thus remain clinically effective. Nevertheless, our work suggests that they be used with caution in this setting.

Nearly 20% of *E. coli* isolates were resistant to enrofloxacin, including 30% of isolates from feces or intestinal tract samples. Similarly, 20% of canine *E. coli* isolates were resistant to enrofloxacin according to a recent study in which investigators evaluated a relatively small number of isolates from various geographic locations in the United States (4). In contrast, investigators evaluating *E. coli* isolates from dogs between 1990–1998 (17) and from dogs and cats between 1989–1997 (32) found a lower prevalence of enrofloxacin resistance, with estimates ranging from 2% to 8%. Thus, enrofloxacin resistance among canine *E. coli* isolates might be increasing over a broad temporal scale. Enrofloxacin was approved for the treatment of bacterial infections in dogs in the United States in 1989, and it is commonly used to treat infections occurring in a wide range of body sites (3). Potential mechanisms of quinolone resistance in *E. coli* include mutations in genes encoding the quinolone target enzymes DNA gyrase and topoisomerase IV (33,34), mutations in genes that regulate the expression of efflux pumps thus resulting in overexpression (35,36), decrease in permeability of the bacterial cell wall (33), and expression of various plasmid-encoded resistance genes such as *qnr* (protection of target enzyme) and *qepA* (efflux pump) (34,37–39).

The occurrence of drug-resistant *E. coli* in dogs represents a potential threat to public health. The role of livestock as a source of pathogen transmission to people has been well-documented, predominantly through foodborne exposure but also via direct contact (40–42). However, dogs generally share the home environment. There are approximately 69.9 million pet dogs in the United States, living in 36.5% of households (43); in Canada, approximately 6.1 million pet dogs live in 32.3% of households (44); 66.7% of people with dogs in the United States consider them to be family members, while another 32.6% consider them to be pets or companions (43). Dogs typically have wide access to the home, including bedrooms and beds (45). Thus, direct contact with dogs is frequent among the human population and could serve as an important route of *E. coli* transmission to humans. In fact, an increasing body of evidence indicates that transfer of resistant bacteria or mobile resistance determinants can occur between dogs and humans (in either direction) through direct contact (46–52). This further underscores the importance of routine hand hygiene following animal contact, particularly among children under the age of 5 years, elderly adults, and immunocompromised persons. It also emphasizes the key role of the veterinarian in zoonotic disease prevention through client education and preventive veterinary care. CVJ

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