Prevalence of Antimicrobial Resistant Bacteria in Dogs Resided in Central Region of Thailand

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Abstract Humans and companion dogs have directly been in close contacts which may pose an important risk of transmitting pathogens and infections. The domestic animals may contribute to antimicrobial resistance problem because antimicrobial resistant bacteria and antimicrobial resistant genes were increasingly found in pets. Thus, the aim of this study was to survey fecal carriage of antimicrobial resistant bacteria in dogs resided in the central region of Thailand. The rectal swabs were taken from 100 apparently healthy dogs (50 stray dogs and 50 household dogs) for bacterial cultures and antibiotic susceptibility testing. The results revealed that an overall prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae in dogs was 35%. ESBL-producing Enterobacteriaceae in fecal carriage in the stray dog samples (62%) was significantly more than the household dog samples (8%), ($p<0.001$). Methicillin-resistant *Staphylococcus aureus* was also isolated from a household dog. *Escherichia coli* isolated from the household dogs tended to be more resistant to some antibiotics than those from the stray dogs. These observations imply that the dogs resided in the central region of Thailand are also the reservoir of antimicrobial resistant bacteria.

Keywords: *Antimicrobial resistant bacteria, ESBL-producing Enterobacteriaceae, household dog, stray dog, Thailand*

บทคัดย่อ **ความชุกของเชื้อแบคทีเรียดื้อยาต้านจุลชีพในสุนัขที่อาศัยอยู่ในเขตภาคกลางของประเทศไทย**

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มนุษย์และสุนัขที่เป็นสัตว์เลี้ยงมีความเกี่ยวข้องสัมพันธ์กันอย่างใกล้ชิด การสัมผัสโดยตรงระหว่างมนุษย์และสุนัขนั้นอาจเป็นปัจจัยที่สำคัญในการถ่ายทอดเชื้อแบคทีเรียก่อโรคระหว่างกันได้ กลุ่มสัตว์เลี้ยงจึงอาจเป็นปัจจัยที่เกี่ยวข้องกับปัญหา

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การดื้อยาต้านจุลชีพ เนื่องจากตรวจพบเชื้อแบคทีเรียและยีนของแบคทีเรียที่ดื้อยาต้านจุลชีพในสัตว์เลี้ยงเพิ่มมากขึ้น ดังนั้น การศึกษานี้จึงมีเป้าหมายในการสำรวจเชื้อแบคทีเรียดื้อยาต้านจุลชีพในอุจจาระของสุนัขที่อาศัยอยู่ในเขตภาคกลางของประเทศไทย สุนัขสุขภาพดีรวม 100 ตัว (สุนัขที่มีเจ้าของ 50 ตัว และสุนัขจรจัดจำนวน 50 ตัว) ถูกเก็บตัวอย่างด้วยวิธี rectal swab เพื่อนำมาจำแนกชนิดของแบคทีเรียและทดสอบความไวต่อยาต้านจุลชีพ ผลการศึกษาพบความชุกของแบคทีเรียชนิด extended-spectrum beta-lactamase-producing (ESBL) Enterobacteriaceae ร้อยละ 35 จากตัวอย่างสุนัขทั้งหมด และพบ ESBL-producing Enterobacteriaceae จากตัวอย่างของสุนัขจรจัด (ร้อยละ 62) มากกว่าสุนัขมีเจ้าของ (ร้อยละ 8) อย่างมีนัยสำคัญทางสถิติ ($p<0.001$) ตัวอย่างหนึ่งที่เก็บจากสุนัขมีเจ้าของยังตรวจพบ methicillin-resistant *Staphylococcus aureus* อีกด้วย ผลการตรวจสอบความไวต่อยาต้านจุลชีพพบว่า เชื้อ *Escherichia coli* ที่พบในตัวอย่างของสุนัขมีเจ้าของมีลักษณะดื้อยาต้านจุลชีพบางชนิดมากกว่าสุนัขจรจัด ผลการศึกษาแสดงว่าสุนัขที่อาศัยอยู่ในเขตภาคกลางของประเทศไทยเป็นแหล่งเก็บกัก (reservoir) เชื้อแบคทีเรียที่ดื้อยาต้านจุลชีพเช่นกัน

คำสำคัญ: *แบคทีเรียดื้อยาต้านจุลชีพ ESBL-producing Enterobacteriaceae สุนัขมีเจ้าของ สุนัขจรจัด ประเทศไทย*

Background and Rationale

Antimicrobial resistance (AMR) problem is considered as one of the most important global health problems that caused high morbidity, mortality, and economic loss. This global health problem may lead to 10 million deaths in humans with a loss of 3% of the world gross domestic product (GDP) by the year 2050.[1] The World Health Organization (WHO) has launched global action plan on antimicrobial resistance since 2015[2] and all member states agreed to develop their own national action plans in line with WHO global action plan within May 2017. Estimation of AMR burden on human health in Thailand revealed that there were 38,000 to 45,000 deaths due to AMR infections per year with an annual economic loss of 0.6% of national GDP[3,4] Antimicrobial resistant bacteria with urgent threat to humans in Thailand were extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae, carbapenem-resistant *Acinetobacter* species (spp.) and *Pseudomonas aeruginosa,* and carbapenem-resistant Enterobacteriaceae. Whereas other AMR bacteria that seriously threaten Thai people include multidrug-resistant *Neisseria gonorrhoeae,* multidrug-resistant *Salmonella, Shigella, Campylobacter* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococci,* and colistin-resistant gram-negative bacteria. One of the key drivers of AMR is inappropriate overuse of antimicrobials in all sectors including human health, animal health, agriculture, and environment. An association of AMR and antimicrobial usage in humans and food animals is a well-known phenomenon.[5,6,7] Some *E. coli* isolates resistant to expanded-spectrum cephalosporin were found to originate from food-producing animals.[8] Therefore, the strategy for prevention and containment of AMR needs multi-sectorial collaboration as 'one health' approach to promote rational use of antimicrobial agents in humans, animals, agriculture, and environment. Antimicrobial resistant bacteria, especially ES-

BL-producing gram-negative bacteria, were commonly isolated in foods and food animals in Thailand.[9,10] The data on public health risk of European countries revealed that AMR bacteria originating from companion animals could be transferred to humans and they might cause adverse health effects. The relation between AMR pathogens in companion animals and AMR infections in humans might be due the fact that they were in close contact.[11,12] The major AMR bacteria in companion animals with high prevalence are MRSA, methicillin-resistant *Staphylococcus pseudintermedius,* vancomycin-resistant *Enterococci,* ESBL- or carbapenemase-producing Enterobacteriaceae, and gram-negative bacteria.[13] Thus the frequency of fecal carriage of antimicrobial resistant bacteria in dogs resided in the provinces located in the central region of Thailand is being monitored. Focusing on the local epidemiology of antimicrobial resistant bacteria in companion animals, it is important to evaluate the magnitude of the problem and the risk of transmission of antimicrobial resistant bacteria from companion animals to humans.

Methodology

The study protocol (No. MUVS-2015-61) received an approval from the Faculty of Veterinary Science-Animal Care and Use Committee (FVS-ACUC).

Characteristics of the dogs: By simple randomization, one hundred apparently healthy dogs from Bangkok (n=5), Nakhon Pathom (n=60), and Nonthaburi (n=35) provinces in Thailand were included. The healthy household dog samples (n=50) were randomly selected from household dogs that attended annual vaccination service in veterinary clinic or hospital. The ages of the household dogs were 5 months to 13 years (mean age 6.28 years). For the household dogs, 22 (44%) were females and 30 (60%) were crossbreeds. Twenty of them (40%) were Chihuahua (2; 4%), Maltese (3; 6%), Pomeranian (1; 2%), Poodle (5; 10%), Shih Tzu (6; 12%), and Thai-ridgeback (3; 6%). The stray dogs (n=50) resided in temples and streets were examined as healthy by veterinarians before the samples were collected. The ages of the stray dogs were 5 months to 10 years (mean age 3.84 years). For the stray dogs, 42 (84%) were females and all of them were crossbreeds.

Sample collection from the dogs for bacterial culture: Rectal swab was performed in each dog using a sterile swab. All rectal swab samples were placed into Cary-Blair transport medium and were sent to the laboratory of Division of Infectious Diseases, Department of Medicine, Faculty of Medicine Siriraj Hospital for bacterial isolation and antibiotic susceptibility test.

Isolation of bacteria and antibiotic susceptibility testing of bacteria: The rectal swab was streaked on McConkey agar supplemented with 4 mg/l of ceftriaxone to detect gram-negative bacteria that might be resistant to third generation cephalosporin. The mannitol salt agar was used to isolate *S. aureus.* Colonies of bacteria grown on agar plates were identified by coagulase, catalase, methylene red, Voges-proskauer oxidase, and indole tests. Hemolysis pattern on blood agar was recorded. The acid production from glucose, lactose and sucrose were determined by Triple Sugar Iron Agar test. Antimicrobial susceptibility tests and their interpretations of the isolated bacteria were performed by disc diffusion method according to CLSI guideline 2014[14] or EUCAST 2016.[15] For the cut-off values of susceptibility of some antibiotics against some bacteria that are not available in CLSI and EUCAST, the inhibition zone diameter values were recorded. The diameter of inhibition zone of more than 11 mm for colistin disc (10 μg) was interpreted according to the National Committee for Clinical Laboratory Standards 1981 guidelines as colistin susceptible.[16] The isolated *E. coli* resistant to cefotaxime (inhibition zone diameter <27 mm) and ceftriaxone (inhibition zone diameter <25 mm) were isolated to determine ESBL production by Modified Double Disc Synergy Test (MDDST).[17] Amoxicillin-clavulanate disc (20/10 μg) was centrally placed on Mueller-Hinton agar plate. Cefotaxime, ceftriaxone, cefpodoxime, and cefepime discs were radially placed 15-20 mm apart. The isolate that had synergic inhibition zone of amoxicillin-clavulanate and cephalosporin disc was considered ESBL-producing Enterobacteriaceae. The *E. coli* (ATCC 25922) was used as a negative control.

Statistical analyses: The data were presented as descriptive statistics. Chi-square statistics was used to compare the rates of antibiotic susceptibility between the bacteria isolated from the household dogs and the stray dogs. The p-value of <0.05 was considered statistically significant.

Results

The percentages of isolated bacteria from all dogs are shown in table 1. Enterobacteriaceae (*E. coli, Klebsiella pneumoniae, Enterobacter* spp., *Citrobacter freundii* and *Edwardsiella tarda*) were observed in 46% of the household dogs and 64% of the stray dogs. *E. coli* was the most common isolated bacteria in the household dogs (32%) and the stray dogs (60%). *P. aeruginosa* was isolated from 12% of the household dogs and the stray dogs. *Acinetobacter baumannii* was isolated from 2% of the household dogs and 14% of the stray dogs. *S. aureus* was isolated from 8% of the household dogs and 4% of the stray dogs.

The overall prevalence of fecal carriage of ESBL-producing Enterobacteriaceae in all dogs was 35% (n=35). The rates of fecal carriage of ESBL-producing Enterobacteriaceae in the household dogs

Table 1 The number of isolated bacteria from household dogs (n=50) and stray dogs (n=50)

Types of dog	Percentage of isolated bacteria			
	Enterobacteriaceae	*P. aeruginosa*	*A. baumannii*	*S. aureus*
Household dogs	46	12	2	8
Stray dogs	64	12	14	4

Table 2 Antibiotic susceptibility of the isolated *Enterobacteriaceae*

Antibiotics (n=54)	Percentage of susceptibility					
	E. coli (n=2)	*K. pneumoniae* (n=2)	*Enterobacter spp.* (n=2)	*C. freundii* (n=1)	*E. tarda*	Total
AMP	0	0	0	0	0	0
AMC	63	50	100	0	0	61
CRO	3	0	0	0	0	3
CAZ	46	50	100	100	100	48
FOX	74	100	100	0	100	79
MEM	100	100	100	100	100	100
SXT	57	50	0	0	100	52
CIP	22	0	0	0	0	20

List of abbreviations (Table 2-6): AMP, Ampicillin; AMC, Amoxicillin-clavulanate; CRO, Ceftriaxone; CAZ, Ceftazidime; FOX, Cefoxitin; MEM, Meropenem; SXT, Trimethoprim-sulfamethoxazole; CIP, Ciprofloxacin; CT, colistin; LVX, Levofloxacin; TE, Tetracycline; E, Erythromycin; DA, Clindamycin

and the stray dogs were 8% (n=4) and 62% (n=31), respectively ($p<0.001$). Antibiotic susceptibility profiles of the isolated Enterobacteriaceae from all dogs are shown in Table 2. All isolates of Enterobacteriaceae were resistant to ampicillin whereas 61% of them were susceptible to amoxicillin-clavulanate. Overall susceptibility of Enterobacteriaceae to ceftriaxone, ceftazidime, and cefoxitin were 3%, 48%, and 79%, respectively. Overall susceptibility of Enterobacteriaceae to ciprofloxacin was 20% whereas 52% of the isolates were susceptible to trimethoprim-sulfamethoxazole. All isolates of Enterobacteriaceae were susceptible to meropenem.

Comparison of antibiotic susceptibility profiles of *E. coli* isolated from the stray dogs and the household dogs are shown in Table 3. *E. coli* isolated from the household dogs tended to be more resistant to some antibiotics than those from the stray dogs.

Table 3 Antibiotic susceptibility of *E. coli* isolated from the stray dogs (n=36) and the household dogs (n=18)

Antibiotics	Percentage of susceptibility	
	Stray dogs	Household dogs
AMP	0	0
AMC	86	17
CRO	0	11
CAZ	53	33
FOX	83	44
MEM	100	100
SXT	61	44
CIP	22	22

Antibiotic susceptibility profiles of isolated *P. aeruginosa* and *A. baumannii* are shown in Table 4. All isolates of *P. aeruginosa* were susceptible to ceftazidime, colistin, and meropenem whereas

Table 4 Antibiotic susceptibility of the isolated *P. aeruginosa, A. baumannii* and *S. aureus*

Antibiotics	Percentage of susceptibility		
	P. aeruginosa (n=12)	*A. baumannii* (n=8)	*S. aureus* (n=6)
CAZ	100	100	N/A
MEM	100	N/A	N/A
CIP	92	100	N/A
CT	100	100	N/A
CRO	N/A	25	N/A
SXT	N/A	75	100
LVX	N/A	N/A	100
TE	N/A	N/A	67
E	N/A	N/A	100
DA	N/A	N/A	100

Note: N/A, not applicable

92% of them were susceptible to ciprofloxacin. All isolates of *A. baumannii* were susceptible to ceftazidime, ciprofloxacin, and meropenem, whereas 25% and 75% of them were susceptible to ceftriaxone and trimethoprim-sulfamethoxazole, respectively.

Antibiotic susceptibility profiles of isolated *S. aureus* are shown in Table 4. One strain of *S. aureus* isolated from a household dog was resistant to cefoxitin and oxacillin indicating that such isolate was MRSA. However, all isolates of *S. aureus* were susceptible to cotrimoxazole (trimethoprim-sulfamethoxazole), levofloxacin, erythromycin, and clindamycin, whereas 67% of them were susceptible to tetracycline.

Discussion

The prevalence of fecal carriage of ESBL-producing Enterobacteriaceae in the dogs resided in the central region of Thailand was high when compared with previous studies. The isolated ESBL-producing *E. coli* had been detected in 6% of fecal samples from 53 healthy dogs in Mexico[18], 15% of fecal samples from 151 healthy dogs in Portuguese Republic[19] and 18.5% of fecal samples from 368 healthy dogs in France.[20] Higher prevalence of ESBL-producing *E. coli* (45%) in fecal samples from 20 healthy dogs was reported in the Netherlands[21] whereas the prevalence of ESBL-producing *E. coli* in fecal samples from 209 dogs living in public gardens in Denmark (1.9%) was much lower.[22]

The rate of fecal carriage of ESBL-producing Enterobacteriaceae in the stray dogs (62%) was significantly much higher than that in the household dogs (8%) in central areas. This finding is in accordance with the previous study in Portugal. Dogs from shelter/breeders were three-fold more likely to be ESBL-producing *E. coli* carriers more than the dogs from private owners.[19] The high prevalence of ESBL-producing *E. coli* in stray dogs (75%) from rural Angola was also reported.[23]

In Thailand, the rate of fecal carriage of ESBL-producing Enterobacteriaceae in the stray dogs is comparable to the rate in healthy adult humans in several areas.[12,24] This could be simply due to the fact that the stray dogs ate the foods, especially raw foods, and drank water from public sources contaminated with ESBL-producing Enterobacteriaceae that were very common in Thailand.[9,10] The reason for the household dogs having much lower prevalence of these resistant bacteria could be consumption of uncontaminated foods and water. However, some household dogs were also colonized with ESBL-producing Enterobacteriaceae in their guts. This observation might be related to consumption of homemade raw diet[17,25,26] and/or receiving inappropriate antimicrobial uses which were reported to be the risk factors for fecal carriage of ESBL-producing Enterobacteriaceae.[25,27,28] MRSA isolated from a household dog and a higher prevalence of *E. coli* resistant to several antibiotics, such as amoxicillin-clavulanate, might be related to prior antimicrobial therapy. However, we did not have information on prior antimicrobial therapy of these household dogs.

The observation on high prevalence of ESBL-producing Enterobacteriaceae from dog fecal carriage in the central region of Thailand has several implications. The dogs colonized with ESBL-producing Enterobacteriaceae could develop the serious AMR infections that need therapy with more active antibiotics against these resistant bacteria.[29,30,31] ESBL-producing Enterobacteriaceae in feces of dogs may be another potential reservoir of antibiotic resistant bacteria and these antibiotic resistant bacteria in dogs could be transmitted to the owners or other related people.[24,32] Therefore, the dog's owner should avoid feeding the dog with raw diet and providing the dog with unnecessary antibiotics. More observations on prevalence of antimicrobial resistant bacteria from stray dog fecal carriage in other regions should be further studied to determine an overall picture of AMR potential reservoir in dogs in Thailand.

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