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Risk factors for canine magnesium ammonium phosphate urolithiasis associated with bacterial infection

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ABSTRACT

Background: With limited information available, the association among urinary tract infections, urease-producing bacteria and the presence of magnesium ammonium phosphate (MAP) urolithiasis in canines in Thailand requires more study.

Objectives: This study aimed to investigate the association between demographic characteristics of canines and the presence of MAP urolithiasis in canines, and to evaluate antimicrobial susceptibility patterns of bacteria isolated from canine uroliths.

Methods: A total of 56 canines admitted for treatment with surgical removal of uroliths were recruited. Demographic characteristics and clinical chemistry data were recorded. Bacteria isolated from the removed uroliths were identified. Chemical compositions of the uroliths were analyzed by Fourier transform infrared spectrometer. Potential risk factors were determined with univariable and multivariable logistic regression analyses.



Results: Of 56 canine urolithiasis, bacteria were isolated from uroliths of 38 canines (27 MAP and 11 non-MAP) but not from uroliths of 18 canines (5 MAP and 13 non-MAP). The most common bacteria found in nidus of MAP uroliths was *Staphylococcus pseudintermedius* (approximately 51%). An antimicrobial resistance was frequently found in Staphylococci isolates (42.86%). Multivariate logistic regression analysis showed that the predictors of MAP urolith in canine urolithiasis were being female ($p = 0.044$; adjusted odds ratio [OR], 10.22; 95% confidence interval [CI], 1.06–98.24) and the positive urolith culture ($p = 0.012$; adjusted OR, 8.60; 95% CI, 1.60–46.30).

Conclusions: Our results indicate that *S. pseudintermedius* (a urease-producing bacterium) is the major causative bacteria of MAP uroliths. A positive urolith culture and being female are risk factors of MAP urolithiasis in canines.

Keywords: Risk factors; dog; magnesium ammonium phosphate; urolithiasis; bacterial infection

INTRODUCTION

Urolithiasis is an important health problem in canines [1-3] with various prevalent national rates: 0.05% in Norway, 0.25% in Sweden [4] and 3% in Ukraine [2]. The relationship

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Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: Uttamamul N, Jitpean S, Tavichakorntrakool R; Data Curation: Uttamamul N, Jitpean S, Tavichakorntrakool R; Formal Analysis: Uttamamul N, Lulitanond A, Tavichakorntrakool R; Funding Acquisition: Tavichakorntrakool R; Investigation: Uttamamul N, Jitpean S, Boonsiri P, Tavichakorntrakool R; Methodology: Uttamamul N, Jitpean S, Lulitanond A, Wonglakorn L, Tavichakorntrakool R; Project Administration: Tavichakorntrakool R; Resources: Jitpean S; Supervision: Tavichakorntrakool R; Validation: Uttamamul N, Jitpean S, Lulitanond A, Boonsiri P, Tavichakorntrakool R; Visualization: Uttamamul N, Jitpean S, Boonsiri P, Tavichakorntrakool R; Writing - Original Draft: Uttamamul N, Tavichakorntrakool R; Writing - Review & Editing: Uttamamul N, Jitpean S, Lulitanond A, Wonglakorn L, Sae-Ung N, Boonsiri P, Daduang J, Tavichakorntrakool R.

between urolith and urinary tract infections (UTIs) is either uroliths with subsequent infections or infection-induced uroliths [5,6]. Infection with urease-producing bacteria is generally associated with magnesium ammonium phosphate (MAP) uroliths [7,8]. A previous study [9] reported that the top two most common bacterial isolates from canines with UTIs were *Escherichia coli* and *Staphylococcus* spp., in order. In another study [10], the top two most common bacteria found in uroliths were *Staphylococcus* spp. and *E. coli*, in order. Interestingly, *S. pseudintermedius* was the most common causative bacteria found in urine and uroliths of the canines [11]. The formation of MAP uroliths is associated with the presence of urease-producing bacteria, such as *Staphylococcus* spp., which are capable of splitting urea into ammonia, increasing the urinary pH and resulting in favorable conditions for MAP crystal formation [12,13]. In Thailand, there is limited information about the association between demographic characteristics and UTI with urease-producing bacteria in MAP urolithiasis.

Therefore, we investigated the association between demographic characteristics of canines and the presence of bacteria in MAP uroliths extensively, and evaluated the antimicrobial susceptibility patterns of bacteria isolated from canine uroliths.

MATERIALS AND METHODS

Sample collection

This study was approved by the Animal Ethics Committee of Khon Kaen University, Khon Kaen, Thailand (ACUC-KKU-25/2560). Written informed consent was obtained from dog owners prior to collection of the specimens.

The urolith samples were collected from 56 dogs (37 males and 19 females) with urolithiasis of the lower urinary tract. The dogs were treated for surgical stone removal by cystotomy and open surgical procedures with sterile techniques at Khon Kaen University Veterinary Teaching Hospital, Faculty of Veterinary Medicine, Khon Kaen University, between May 2017 and August 2018. The exclusion criteria of canines included (1) nephrolithiasis, (2) active UTIs or other infections within 1 year prior to admission, (3) history of antibiotic treatment of UTIs within 14 days prior to urine collection for bacterial culture and (4) no permission from the owner.

Isolation and identification of bacteria

To minimize the effect of bacterial culture, all urolith samples were analyzed within one hour after collection. The largest urolith samples were washed several times with deionized water and each urolith was then divided into two parts, as equal as possible [5]. For the first part, the nidus portion of uroliths obtained by scraping was cultured on blood and MacConkey agar at 35°C–37°C for 18–24 h. Each different bacterial colony was also considered as a significant bacterial isolate for further identification by conventional biochemical tests [14] and antimicrobial susceptibility testing. The species of Staphylococci was confirmed by VITEK 2 automated microbiology system (bioMérieux, Marcy l'Etoile, France). All bacteria isolates were determined to be urease-producing by Christensen's urea agar. Moreover, all isolates of *S. pseudintermedius* were confirmed by urease activity assay kit (MAK120; Sigma Aldrich, USA).

Antimicrobial susceptibility test

All bacterial isolates with different morphological characteristics were analyzed for their antimicrobial susceptibility using the disk diffusion method according to the standard method

of the Clinical and Laboratory Standards Institute (CLSI) 2017 [15]. They were cultured on Mueller-Hinton agar (Oxoid, England) and incubated at 37°C for 18-24 h. The antimicrobial disks used in this study included amikacin (AK 30 µg), gentamicin (CN 10, 120 µg), amoxicillin-clavulanic acid (AMC 20/10 µg), piperacillin/tazobactam (TZP 110 µg), ampicillin (AMP 10 µg), doxycycline (DO 30 µg), tetracycline (TE 30 µg), trimethoprim/sulfamethoxazole (SXT 1.25/23.75 µg), cefazolin (KZ 30 µg), cefotaxime (CTX 30 µg), ceftazidime (CAZ 30 µg), ceftiofur (FOX 30 µg), norfloxacin (NOR 10 µg), ofloxacin (OFX 5 µg), ciprofloxacin (CIP 5 µg), enrofloxacin (ENR 5 µg), fosfomycin (FOS 200 µg), fusidic acid (FA 10 µg) and vancomycin (VA 30 µg).

Analysis of chemical compositions of urolith

The second part of each urolith sample after bacterial culture was ground into a powder, and then the chemical composition was analyzed by Fourier transform infrared (FTIR) spectrometer (model ALPHA; Bruker, Germany) with a resolution of 4 cm⁻¹ and measurement range of 4,000 to 650 cm⁻¹. The FTIR spectra of each sample were analyzed in triplicate and data were compared to Bruker's BLG 1 and 2 spectral libraries for chemical composition of uroliths. Whole parts of a urolith containing ≥ 70% of a single mineral type were identified by that mineral type. The mineral types with less than 70%, were classified as a mixed urolith [3].

Statistical analysis

Statistical analysis was performed on data including sex, age range, breed, urine pH, blood test, urolith size, bacterial culture results and chemical composition of the urolith. The normality tests of the continuous data were assessed by the Shapiro-Wilk test. The student *t*-test and Wilcoxon rank sum test were used to assess normally and non-normally distributed continuous data outcomes, respectively. The normal distribution data were expressed as mean with standard deviation (mean ± SD) while the non-normal distribution data were expressed as median with interquartile range (IQR). The Chi-squared or Fisher's exact tests were used to compare categorical data outcomes. The associations between potential risk factors and outcome were examined by means of univariate logistic regression. All variables with *p* values < 0.25 in the univariate analysis were included in subsequent multivariate logistic regression analyses. All variables with *p* values > 0.20 in the multivariate model were excluded with the stepwise approach, whereas those with *p* values < 0.10 were retained in the final model. Analytical results were presented as adjusted odds ratio (OR) and 95% confidence interval (CI). Statistical significance is defined as a *p* value < 0.05. Statistical analyses were performed using STATA version 10.1 software (STATA Corp., USA).

RESULTS

A total of 56 (37 males and 19 females) canines with urolithiasis were included in the present study. The mean age of all dogs was 7.29 ± 3.43 years. The grouping with a range of less than 10 years had 40 (71%) dogs while that equal or greater than 10 years had 16 (29%) dogs. There were 38 (68%) small breeds (Shih Tzu, Chihuahua, Pomeranian, Pug, Miniature Poodle, Beagle, Miniature Pinscher and English Cocker spaniel), 3 (5%) large breeds (Golden Retriever and Siberian Husky) and 15 (27%) mixed breeds.

The major chemical compositions of canine uroliths were 32 with MAP (57%), 13 with calcium oxalate (23%), eight with mixed compounds (14%), one with cystine (2%), one with uric acid (2%) and one with calcium phosphate (2%). MAP uroliths were the most common type and were found in 17 females (53%). Of 32 dogs with MAP uroliths, 18 dogs were small-

sized breeds (56%) [Shih Tzu (22%), Poodle (13%), Chihuahua (6%), Pug (6%), Pomeranian (3%), Beagle (3%) and Miniature Pinscher (3%)], 11 were mixed breeds (34%) and three were large breed (9%) dogs.

The demographic characteristics and clinical chemistry data of all dogs are summarized in **Table 1**. All parameters of age range, urine pH, white blood cell (WBC) count and serum creatinine showed no statistically significant differences between MAP and non-MAP uroliths ($p > 0.05$). On the other hand, sex, breed, blood urea nitrogen (BUN), urolith size and bacterial culture from urolith showed significant differences between MAP and non-MAP uroliths ($p < 0.05$).

Chemical compositions of a total of 56 canine uroliths and bacterial culture analyses revealed that the most common urolith type with bacterial isolates was MAP ($n = 27$, 71%), whereas that for uroliths without bacterial growth was calcium oxalate ($n = 10$, 56%). A total of 56 uroliths, 38 samples (27 MAP and 11 non-MAP) were positive for bacterial culture, and the others (5 MAP and 13 non-MAP) were negative. More than one bacterial species isolated was found in 10 of 27 MAP uroliths and 6 of 11 non-MAP uroliths. The top five most common bacteria found in the nidus of MAP uroliths were *S. pseudintermedius* ($n = 20$, 51.28%), *E. coli*, ($n = 4$, 10.26%), *Proteus mirabilis* ($n = 3$, 7.69%), *Pseudomonas aeruginosa* ($n = 2$, 5.13%) and *Klebsiella pneumoniae* ($n = 1$, 2.56%) (**Table 2**). Furthermore, urease test on the bacteria, isolated from 27 MAP uroliths, revealed that the urease-producing bacteria had been isolated from 25 MAP uroliths (93%). To address this, antimicrobial susceptibility was tested. The data showed that the bacteria isolated from the nidus of uroliths had an antimicrobial resistance. Nine of 21 (42.86%) Staphylococci isolates had antimicrobial resistance. All isolates of *E. coli*, *P. mirabilis* and *K. pneumoniae* had multidrug resistance (**Table 2**).

Because there was significant difference between some characteristics of MAP urolith formers and non-MAP urolith formers (**Table 1**), potential risk factors in canines with MAP

Table 1. Demographic characteristics and clinical chemistry data from canines with urolithiasis

Parameters	Urolith formers (total $n = 56$)		p value
	MAP ($n = 32$): n (%)	Non-MAP ($n = 24$): n (%)	
Sex			< 0.001
Male	15 (40.54)	22 (59.46)	
Female	17 (89.47)	2 (10.53)	
Age range			0.932
< 10 years	23 (57.50)	17 (42.50)	
≥ 10 years	9 (56.25)	7 (43.75)	
Breed			
Small	18 (47.37)	20 (52.63)	0.032
Large	3 (100.00)	0 (0.00)	0.252
Mixed	11 (73.33)	4 (26.67)	0.139
Urine pH, median (IQR)	7.50 (7–8)	7 (6–8)	0.192
Blood tests			
WBC (10^3 /uL), median (IQR)	14.90 (9.60–24.50)	10.2 (7.80–18.9)	0.148
BUN (mg/dL), median (IQR)	27 (22–51.90)	17.25 (12–23)	0.036
Creatinine (mg/dL), median (IQR)	0.85 (0.58–1.39)	0.63 (0.55–0.90)	0.215
Urolith size			
Width (mm), median (IQR)	8.56 (4–21.77)	3.37 (2.60–4.51)	0.001
Length (mm), median (IQR)	11.07 (5.40–26.62)	4.52 (3.07–6.79)	< 0.001
Bacterial culture from urolith			0.002
Positive	27 (71.05)	11 (28.95)	
Negative	5 (27.78)	13 (72.22)	

MAP, magnesium ammonium phosphate; IQR, interquartile range; WBC, white blood cell; BUN, blood urea nitrogen.

Table 2. Antimicrobial resistance (%) of the top five most common bacteria (n = 31) isolated from nidus of MAP uroliths

Bacteria isolated from nidus of MAP uroliths	Antimicrobial resistance (%)																							
	CN	DO	TE	SXT	KZ	FOX	OFX	FOS	FA	AK	AMC	TZP	AMP	DO	SXT	KZ	CTX	CAZ	NOR	OFX	ENR	CIP	FOS	
Staphylococci																								
<i>S. pseudintermedius</i> (n = 20)	15	5	35	25	15	5	25	0	0															
<i>S. aureus</i> (n = 1)	0	0	100	0	0	0	0	0	0															
Enterobacteriales																								
<i>E. coli</i> (n = 4)	0	25	25	25	75	75	50	25	0	0	25	25	25	25	0									
<i>P. mirabilis</i> (n = 3)	0	33	33	0	67	100	67	33	33	0	67	67	100	67	0									
<i>K. pneumoniae</i> (n = 1)	0	100	100	0	100	100	100	100	100	100	100	100	100	100	100									
Non fermentative Gram-negative bacilli																								
<i>P. aeruginosa</i> (n = 2)	0	0	0	100	0	0	50																	
Total (n = 31)																								

MAP, magnesium ammonium phosphate; CN, gentamicin; DO, doxycycline; TE, tetracycline; SXT, trimethoprim/sulfamethoxazole; KZ, cefazolin; FOX, ceftiofur; OFX, ofloxacin; FOS, fosfomicin; FA, fusidic acid; AK, amikacin; AMC, amoxicillin-clavulanic acid; TZP, piperacillin/tazobactam; AMP, ampicillin; CTX, cefotaxime; CAZ, ceftazidime; NOR, norfloxacin; ENR, enrofloxacin; CIP, ciprofloxacin.

urolithiasis were also determined with univariate analysis (**Table 3**) and multivariable logistic regression analyses (**Table 4**), respectively. Univariate analysis showed significant association of sex, urolith size and bacterial culture from urolith in canines with MAP urolithiasis. Multivariate logistic regression analysis (**Table 4**) showed that the predictors of MAP urolith in canine urolithiasis were being female ($p = 0.044$, adjusted OR, 10.22; 95% CI, 1.06–98.24) and the positive urolith culture ($p = 0.012$, adjusted OR, 8.60; 95% CI, 1.60–46.30).

Table 3. Univariate analysis for association between various factors and magnesium ammonium phosphate uroliths in canine urolithiasis

Parameters	OR	95% CI	p value
Sex			
Male	1	-	-
Female	12.47	2.50–62.08	0.002
Age range			
≥ 10 years	1	-	-
< 10 years	1.05	0.33–3.39	0.932
Breed			
Small	1	-	-
Mixed	2.62	0.72–9.59	0.146
Large	-	-	-
Urine pH	1.56	0.84–2.90	0.158
Blood tests			
WBC ($10^3/\mu\text{L}$)	1.06	0.98–1.14	0.136
BUN (mg/dL)	1.00	0.99–1.02	0.605
Creatinine (mg/dL)	0.92	0.69–1.22	0.569
Urolith size			
Width (mm)	1.19	1.04–1.36	0.013
Length (mm)	1.16	1.03–1.30	0.012
Bacterial culture from urolith			
Negative	1	-	-
Positive	6.38	1.83–22.21	0.004

OR, odds ratio; CI, confidence interval; WBC, white blood cell; BUN, blood urea nitrogen.

Table 4. Multivariate analysis for factors associated with magnesium ammonium phosphate urolith in canine urolithiasis

Parameters	Adj. OR	95% CI	p value
Sex (female)	10.22	1.06–98.24	0.044
Urolith size			
Width (mm)	1.00	0.66–1.54	0.985
Length (mm)	1.05	0.73–1.51	0.797
Bacterial culture from urolith (positive)	8.60	1.60–46.30	0.012

Adj. OR, adjusted odds ratio; CI, confidence interval.

DISCUSSION

In our study, the top two most common chemical compositions for the canine uroliths were MAP (57%) and calcium oxalate (23%), in order. This observation in Thailand is consistent with other findings that the most common urolith in canines was MAP [1,3]. In strong evidence, we also found that the important risk factors of MAP uroliths were female-sex and positive urolith culture. The main risk factors for developing canine MAP urolithiasis may depend on several factors such as UTIs, being female, and small-sized breeds (Miniature Schnauzer, Shih Tzu, Bichon Frise, Miniature Poodle) [7]. The present study indicated that the most common bacteria found in the stone nidus of the MAP urolith was *S. pseudintermedius*, all of which are urease-producing bacteria. The urease activity of these bacteria isolates was evaluated by Christensen's urea agar and confirmed by the urease activity assay kit. This finding agrees with other studies in terms of MAP uroliths in canines being mainly caused by urease-producing bacterial infection [7,16]. We speculated that the *S. pseudintermedius* found in the nidus of uroliths is the causative bacteria involved in the MAP urolith formation and pathogenesis. Uroliths can also act as a nidus for infection and can be found in canines with recurrent UTIs [10,17].

From a total of 21 Staphylococci isolates, nine isolates (42.86%) had antimicrobial resistance. In addition, *S. pseudintermedius*, *E. coli*, *P. mirabilis* and *K. pneumoniae* had multidrug resistance (Table 2). This dataset indicates the high percentage and patterns of antimicrobial resistance in Enterobacterales (*E. coli*, *P. mirabilis* and *K. pneumoniae*) isolated from the stone nidus of canine uroliths. The mechanism of multidrug resistance in Gram-negative bacteria may affect the permeability barrier function of their outer membrane [18,19], biofilm formation [20], horizontal spread of antimicrobial resistance genes and clonal selection of resistance strains in recurrent UTIs [21,22].

According to previous research, MAP uroliths often occur in alkaline urine, which is often caused by urease-producing bacteria [12,13,23]. However, the urinary pH in the canines with MAP uroliths was 7.5, which was not significantly different from non-MAP uroliths ($p > 0.05$) (Table 3). The possible explanation may be the food components and water consumption that causes MAP uroliths [24]. Moreover, our data showed that the risk factors of MAP urolithiasis were being female and positive urolith culture (Table 4).

Nevertheless, limitations of our present study should be noted. Firstly, we selected only the largest size of urolith for both bacterial culture and chemical composition analysis. Secondly, chemical composition analysis of whole uroliths was done. Therefore, stone core or nidus chemical composition analysis could not be interpreted separately. Thirdly, data on the type of primary diet and recurrent urolith formers are not available. Fourthly, some owners may have misclassified known breeds as mixed breeds. Lastly, the detection of methicillin resistance in *S. pseudintermedius* by oxacillin disk is recommended instead of cefoxitin disk.

In summary, *S. pseudintermedius* (a urease-producing bacteria) is the major causative bacteria of MAP uroliths. A positive urolith culture and being female are risk factors of MAP urolithiasis in canines. In addition, this study provides information about the bacterial species and antimicrobial susceptibility patterns in canines with urolithiasis. According to the guidelines for diagnosis and treatment of UTI from the International Society for Companion Animal Infectious Diseases (ISCAID), antimicrobial susceptibility testing of bacteria causing

recurrent canine cystitis associated with urolithiasis is strongly recommended and needs to be performed for systemic antimicrobial treatment.

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