Original Article

Clinical investigation of feline lower urinary tract disease, pathogenic bacteria and their antibiotic sensitivity at University Veterinary Hospital, Universiti Putra Malaysia

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Abstract

This study describes the clinical manifestation, bacterial pathogens and antibiotic sensitivity in cats diagnosed with Feline lower urinary tract disease (FLUTD). A total of 61 cats diagnosed with FLUTD from 2018 to 2019 were included in this study. Medical records were reviewed and rational antibiotic therapy was calculated from the data collected on antibiotic sensitivity. Most cats in this study belonged to indoor multi-cat households with shared facilities. Thirty-two cats (52.45%) had positive urine cultures and were diagnosed with urinary tract infections. *Staphylococcus* species (23.2%), *Enterococcus* species (17.9%) and *Escherichia coli* (16.1%) were the most isolated bacteria. *Escherichia coli* demonstrated high levels of resistance to tested antibiotics, signifying the presence of resistant strains in Malaysia. The antibiotic impact factor calculated was 31.14 for cephalexin, 30.83 for amoxicillin/clavulanic acid, 19.82 for enrofloxacin and 19.43 for ceftriaxone. This study highlights the significance of urine culture and susceptibility testing prior to antibiotic administration. Based on the results of this study, empirical treatment can be provided based on the bacterial spectrum and the antibiotic impact factor.

Keywords: FLUTD, ultrasonography, radiology, bacteria, antibiotic sensitivity

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Introduction

Feline lower urinary tract disease (FLUTD) is a collection of conditions that affect the cat urinary bladder and urethra. It can be caused by uroliths, urethral plugs, bacterial infections, bladder neoplasia or idiopathic cystitis (Martinez-Ruzafa *et al.*, 2012; Sævik *et al.*, 2011). Clinical signs of FLUTD include haematuria, stranguria, dysuria, periuria and/or pollakiuria, present with or without obstruction. The prevalence of FLUTD ranges from 1.6% to 16.4% in the feline population presented to veterinary practices globally (Bartges, 1997; Gama *et al.*, 2009; Gerber *et al.*, 2005; Kirk *et al.*, 2001; Lekcharoensuk *et al.*, 2001; Nururrozi *et al.*, 2020; O'Neill *et al.*, 2014; Piyarungsri *et al.*, 2020).

Feline idiopathic cystitis (FIC) is the leading cause of FLUTD accounting for about 55% to 60% of cases, followed by urolithiasis (12-22% of cases) and bacterial urinary tract infections (UTIs) (1.5-20% of cases) (Dorsch *et al.*, 2014; Eggertsdóttir *et al.*, 2007; Gerber *et al.*, 2005; Lew-Kojrys *et al.*, 2017; Sævik *et al.*, 2011). A thorough diagnostic workup of FLUTD is required to identify the specific aetiology to optimise treatment. Diagnostic tests consist of urinalysis, haematology, serum biochemistry, diagnostic imaging techniques such as radiography, ultrasonography, urine culture and susceptibility. A diagnosis of FIC is made by exclusion only when no other specific aetiology can be identified (Buffington, 2011; Forrester & Towell, 2015; Sævik *et al.*, 2011).

FLUTD treatment includes anti-inflammatory drugs, anti-spasmodic drugs, pain management and catheterisation in blocked cats. The latest guidelines for the management of feline and canine UTIs recommend the use of trimethoprim-sulphonamide, amoxicillin or amoxicillin/clavulanic acid in cases of UTIs (Weese *et al.*, 2019). This recommendation is based on the global leading bacteria and their sensitivity towards these antibiotics.

Monitoring of urinary pathogens and their susceptibility patterns help in the selection of empirical antibiotic therapy and to record the presence of resistant bacteria within the country.

This study aims to clinically investigate cases of FLUTD, identify the pathogens causing UTIs in the feline population presented to the University Veterinary Hospital, Faculty of Veterinary Medicine, Universiti Putra Malaysia, and to further investigate their antibiotic sensitivities. The antibiotic impact factors and antibiogram produced can then be used to formulate local empirical treatment recommendations for veterinarians and provide baseline data for antibiotic resistance status.

Materials and Methods

Selection of cases: Medical records for cats diagnosed with FLUTD at the University Veterinary Hospital, Faculty of Veterinary Medicine, Universiti Putra Malaysia between January 2018 and December 2019 were reviewed. Inclusion criteria for the cases required patients to have complete records, with at least one imaging technique either ultrasonography or radiology, urine culture and sensitivity results. Data available including sex, age, breed, management (indoor or outdoor), single or multicat household were recorded. History and clinical presentation including rectal temperature, presenting clinical signs like stranguria, and physical examination findings such as non-compressible bladder and urethral plugs were also evaluated. Haematology, serum biochemistry, urinalysis, urine culture and antibiotic sensitivity test results were retrieved and evaluated.

Diagnostic imaging: Patient radiographs and/or ultrasonograms were reviewed and evaluated by two veterinarians to reach a consensus. Lateral and ventrodorsal views of abdominal radiographs were evaluated for the presence of stones within the urinary tract and any other abnormalities. The location, size, opacity and presence of radio-opaque stones or gas accumulations in the urinary tract were recorded. Abdominal ultrasonographic images were evaluated based on the bladder wall thickness (ventral and dorsal) recorded on moderately distended bladders, presence of membranes or clots, presence of sediments/crystals and presence of stones with shadowing. Contrast radiography was performed in cats in which plain radiography and ultrasonography did not provide an adequate diagnosis. Urethrography was conducted using iohexol (100-150 mg/ml).

Bacteria culture and antimicrobial susceptibility: Patient urine culture and antimicrobial susceptibility results were retrieved. Urine samples were collected either via cystocentesis or from the urinary catheter upon admission. The samples were cultured on 5% horse blood and MacConkey agar plates and incubated for 24 to 48 hours at 37 ^{0}C in aerobic conditions. Bacterial species were identified by performing conventional biochemical tests. Data was recorded based on the type of culture (either single or multiple colonies) and the bacterial species isolated. Meanwhile, antimicrobial susceptibility was tested via the Kirby Bauer technique and the results were recorded.

Impact factor calculation: Antibiotic impact factor describes the likelihood that a bacterial pathogen would be sensitive to an antibiotic. The higher the value, the more likely bacteria are sensitive to the antibiotic. It is based on in vitro susceptibility testing and is calculated by the formula to select rational antibiotic therapy (FRAT) (Blondeau & Tillotson, 1999).

According to FRAT the impact factor (IF) of a specific antibiotic, is the sum of the total impact factor (if) of the antibiotic on each pathogen. Impact factor (if) for a pathogen is calculated by multiplying the prevalence of the pathogen (P) and by the proportion of the isolates sensitive to that respective antibiotic (S). This process is repeated for each major bacterial species that may be present. IF is the sum of impact factors (if) derived for each species:

$$\mathrm{If}_1 = = (P_1\% \ x \ S_1\%)/100$$

$$IF = (P_1\% \ x \ S_1\%)/100 + (P_2\% \ x \ S_2\%)/100 + (P_3\% \ x \ S_3\%)/100 + \ldots n$$

$$IF = \sum \ (P\% \ \mathrm{X} \ S\% \ )/100$$

IFs were evaluated for the 4 antibiotics based on ISCAID guidelines (Weese *et al.*, 2019) and the availability of drugs at the hospital.

Treatment and outcomes: Data was collected on the management and treatment, either medical or surgical. Recovery and outcome were evaluated based on their records during the hospitalisation period. Patients were recorded as recovered when they were discharged without any clinical signs. All materials and methods were consistent throughout the study period.

Result

Signalment and history: A total of 61 cats (52 males, 9 females) diagnosed with FLUTD (2018-2019), aged from 1 year to 10 years (mean: 3.68 years ± 2.43) were included in this study (see Table 1). Most of the cats (n = 51) were domestic short hair, whereas five were Maine coon, four were Persian and one was Himalayan. The majority of the cats belonged to multi-cat households (n = 49) and were managed as completely indoor pets (n = 45) compared to those belonging to a single cat household (n = 12) and having outdoor access (n = 16).

Table 1 Patient signalment of 61 cats diagnosed with FLUTD.

Patient signalment	Number of cats (n)	Percentage (%)
Male	52	85.2
Intact male	31	50.8
Castrated male	21	34.4
Female	9	14.8
Intact female	5	8.2
Spayed female	4	6.6
Breed		
Domestic Short-haired	51	83.6
Himalayan	1	1.6
Persian	4	5.6
Maine coon	5	8.2
Managed indoors	45	73.8
Number of cats in a household		
Single cat household	12	19.7
Multi-cat household	49	80.3

Clinical presentation and physical examination: Thirteen cats were dull and depressed, 48 (78.7%) and 28 (45.9%) cats were presented with stranguria and haematuria, respectively. History revealed that 29 cats (47.5%) had reduced appetite and 15 (24.6%) had episodes of vomiting. A higher proportion (68.9%; n = 42) of the cats were presented for their first episode of urinary tract problems, while 31.1% (n = 19) were present for recurrent episodes. The duration between episodes ranged from 1 month to 4 years.

The mean rectal temperature recorded was 37.8 ± 1.1 ºC (RR: 38.1-39.2 ºC), ranging from 33.4 ºC to 39.3 ºC. Upon palpation, a higher proportion (75.4%; n = 46) of the cats had a turgid abdomen, 26 of them had non-compressible bladders, with urethral plug present only in nine cats.

Haematological and biochemical results: Neutrophilia was recorded in 35 (63.0%) cases, of these, a left shift was reported in 26 (56.5%) cases. Meanwhile, leucocytosis and monocytosis were reported in 30 (53.6 %) and 27 cats (48.2%), respectively. Thrombocytopenia was recorded in 10 (34.5%) samples while two cats (3.6%) had lymphocytosis. Elevated urea and creatinine values were reported in 39 (70.2%) and 25 cats (49.1%), respectively. Of these, 32 cases were presented with stranguria suggesting post-renal azotaemia. Based on follow-up CBC and serum biochemistry results from 5 to 7 days later, 14 of the 32 cases revealed normal urea and creatinine levels. Other noteworthy biochemical results included hyperkalaemia (n = 19; 39.2%), hypochloraemia (n = 12; 24.5%), hyperphosphatemia (n = 12; 39.4%).

Urinalysis results: Urine samples for urinalysis were collected upon admission, before any treatment was administered. Urinalysis revealed proteinuria in 47 cats (85.5%), microscopic haematuria in 46 cats (83.6%) (normal range < 10 cells/hpf) and pyuria (> 5 WBC/hpf) in 32 cats (58.2%). The mean urine SG recorded was 1.0277 ± 0.011 and the median SG was 1.0270. Three cats (5.6%) had high acidic urine than normal (< 6.0), 15 cats (28.3%) had alkaline urine (> 6.5), whereas crystals were reported only in 14 cats (25.9%).

Nine cats had triple phosphate crystals (struvite) of which only five had positive urine cultures. Meanwhile, three cats showed the presence of amorphous urates of which one had positive urine culture results. One cat each recorded the presence of calcium oxalate and amorphous phosphate crystals and both had positive urine culture results. Bacteriuria was identified in 27 urine sediment samples.

Radiology findings: The abdominal radiographs (lateral and VD views) of 21 cases were evaluated. Emphysematous cystitis was identified in two cats (Fig. 1) and uroliths were diagnosed in two cats (Fig. 2). Nine cases had inconclusive plain radiography results and a contrast study with iohexol (100-150 mg/ml) was performed. Urethral stenosis and bladder leakage were diagnosed in seven and three cats, respectively. Only a single case of urethral stenosis concurrent with bladder leakage was diagnosed in this study.

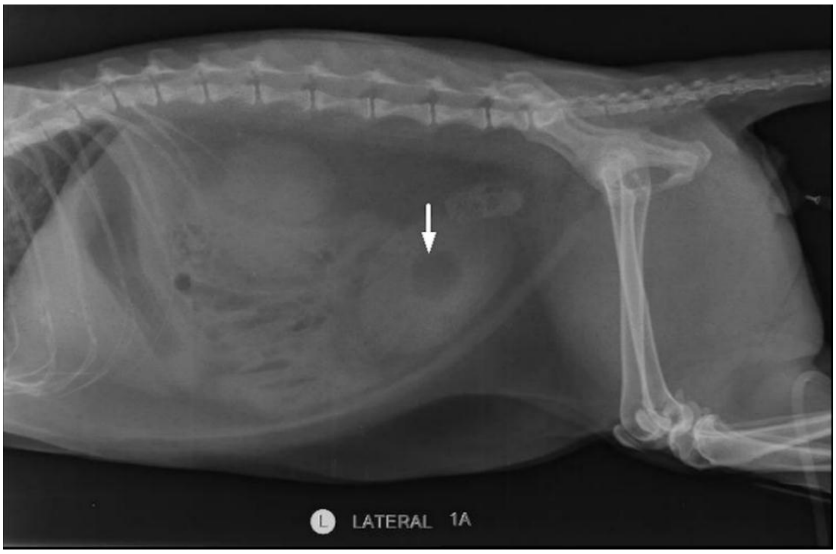

Figure 1 Left lateral abdominal radiograph of a cat. Rounded gas opacity within the bladder (white arrow) seen in a case of emphysematous cystitis.

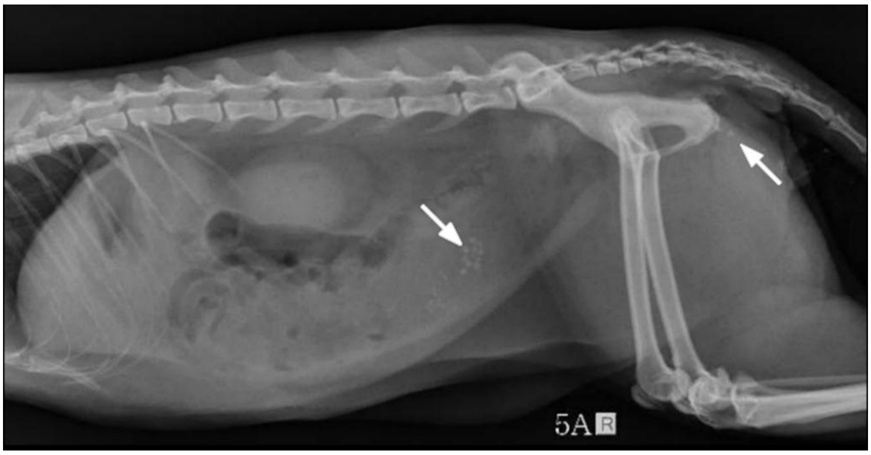

Figure 2 Right lateral abdominal radiograph of a cat. Uroliths within the bladder and urethra (white arrows).

Ultrasonography findings: Ultrasonographic evaluations of 45 cats revealed a thickened bladder wall with a mean ventral bladder wall thickness of 3.47 ± 2.05 mm and dorsal bladder wall thickness of 3.11 ± 1.42 mm (reference range: 1.33-1.77mm). Crystals/cells/sediment were present in 15 (24.6%) cases while clots and/or membranes were present in 16 (26.2%) cases. In six (13.3%) cases crystals were present along with clots and/or membranes (Fig. 3-a). Uroliths and emphysematous cystitis were observed only in a single case each (22.2%) (Fig. 3-b).

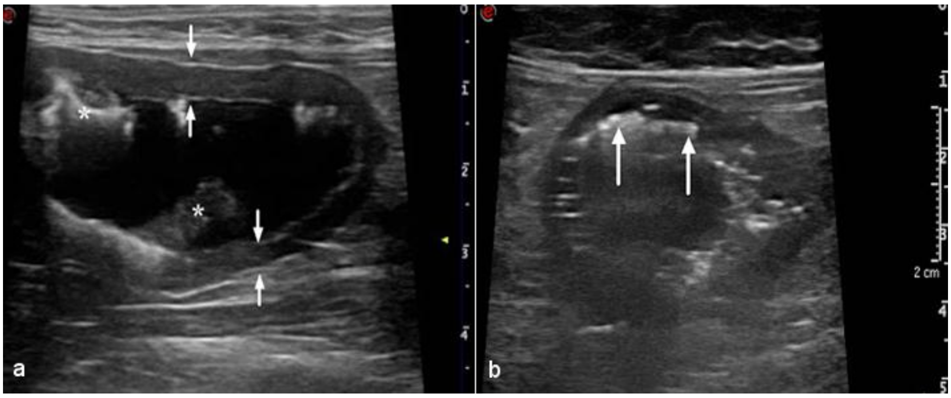

Figure 3(a) Sagittal view of feline bladder ultrasound. The bladder visible with thickened bladder wall (white arrows) and presence of clots/membranes (White*).

Figure 3(b) Sagittal view of feline bladder ultrasound. Bladder visible with hyperechoic foci (white arrowhead) consistent with gas within the bladder wall, seen in a case of emphysematous cystitis.

Bacteria Culture: Out of 61 urine cultures, 29 (47.5%) samples showed no growth, 17 (27.9%) were positive for a single colony of bacteria and 15 (24.6%) had multiple colonies. Of these, 73.3% of the positive samples were collected via cystocentesis, 13.3% were via urinary catheter and 13.3% were via manual compression.

A total of 56 bacterial isolates were found. *Enterococcus faecalis* was the leading bacteria in multiple colony growths at 42.8%, while *Proteus mirabilis, Klebsiella pneumoniae* and *Escherichia coli* were the leading pathogens in single colony growths at 16% each. The leading species isolated from 61 samples were *Staphylococcus* species (23.2%) followed by *Enterococcus* species (17.9%), *E. coli* (16.1%) and *K. pneumoniae* (12.5%) (Table 2).

Table 2 Bacteria isolated from 32 positive urine culture results.

Bacteria	Number of isolates (n)	Percentage (%)
Staphylococcus species	13	23.2
Staphylococcus pseudintermedius	7	12.5
Staphylococcus intermedius	5	8.9
Staphylococcus schleiferi	1	1.8
Enterococcus faecalis	10	17.9
Escherichia coli	9	16.1
Klebsiella pneumoniae	7	12.5
Proteus mirabilis	4	7.1
*Enterobacte*r species	3	5.4
Enterobacter cloacae	2	3.6
Enterobacter aerogenes	1	1.8
Pseudomonas species	3	5.4
Pseudomonas aeruginosa	2	3.6
Pseudomonas fluoresceus	1	1.8
Salmonella enterica	2	3.6
Acinetobacter baumanii	2	3.6
Streptococcus dysgalactiae	1	1.8
Aeromonas species	1	1.8
Pasteurella pneumotropica	1	1.8
Total	56	100

Antimicrobial Sensitivity: The Formal for Rational Antibiotic Therapy (FRAT) was used to calculate the impact factor for cephalexin, amoxicillin/clavulanic acid, enrofloxacin and ceftriaxone. This selection was based on the four commonly used antibiotics to treat feline UTI (Weese *et al.*, 2019) and antibiotic sensitivity results of the seven most common pathogens as reported in Table 2. Cephalexin recorded the highest impact factor of 31.14, closely followed by amoxicillin/clavulanic acid at 30.83 (Table 3).

Based on the antibiotic susceptibility results (Table 4), *Staphylococcus* species was most sensitive to cephalexin (100%) and was closely followed by amoxicillin/clavulanic acid (80%). *Enterococcus* species showed 62.5% sensitivity towards amoxicillin/clavulanic acid. *E. coli* was the most sensitive to ceftriaxone (50%) but highly resistant to enrofloxacin (100%).

Table 3 Impact factor of commonly administered antimicrobials using FRAT

Antibiotic	Impact Factor
Cephalexin	31.14
Amoxicillin/Clavulanic acid	30.83
Enrofloxacin	19.82
Ceftriaxone	19.43

Table 4 Antibiotic susceptibility for the most prevalent feline urinary isolates (Antibiogram)

Bacteria (%)	Amoxicillin/ clavulanic acid	Enrofloxacin	Cephalexin	Ceftriaxone
Staphylococcus spp. (23.2%)	80	44.4	100	11.1
Enterococcus faecalis (17.9%)	62.5	12.5	28.5	20
Escherichia coli (16.1%)	20	0	25	50
Klebsiella pneumoniae (12.5%)	0	0	0	40
Proteus mirabilis (7.1%)	20	40	25	25
Pseudomonas spp. (5.4%)	0	50	0	0
Enterobacter spp. (5.4%)	0	0	0	0

Treatment and outcome: A higher proportion of the cases (82%; n = 50) were resolved medically. A urinary catheter was placed for 35 (55.7%) cats for an average of 6.2 days. All cats were treated with antibiotics, based on the hospital protocol for FLUTD management while awaiting urine culture results. Antibiotic choice was based on guidelines by ISCAID (Weese *et al.*, 2019), urine culture sensitivity results and availability of drugs. 72.1% were treated with amoxicillin / clavulanic acid, 14.8% with cephalexin, 9.8% with enrofloxacin, 1.6% with doxycycline and cefixime each. Six catheterised cats and five non-catheterised cats required surgical intervention due to either urethra blockage or stenosis, bladder rupture or uroliths. The three non-catheterised cats that underwent perineal urethroscopy were catheterised post-operatively Most of the catheterised cats (n = 31) made a full recovery, two were euthanised due to cost constraints from the owner and one cat succumbed to the condition. Overall, 25 non-catheterised cats made a full recovery and two succumbed to the condition. The average hospitalisation period was 8.9 days.

Discussion

Slightly more than half (52.5%) of the 61 cats included in this study were diagnosed with UTI. This is higher than previous reports where bacterial UTIs ranged from 1.5% to 20% (Dorsch *et al*., 2014; Eggertsdóttir *et al*., 2007; Gerber *et al*., 2005; Lew-Kojrys *et al*., 2017; Sævik *et al*., 2011). The current study included a mixture of first opinion and referral cases. A study conducted in the United States found that fewer than 3% of the cat population were diagnosed with UTI (Kruger *et al*., 1991), which could be attributed to the fact that most cases included in the study were referral cases. In contrast, a previous study conducted by Saevik *et al*. (2011), included mainly first opinion cases and found only 15.1% cases with UTI. These disparities could be due to factors such as inclusion criteria, the difference in geographical locations, management trends, cats' lifestyles and the owners' awareness.

The mean age recorded in this study was 3.68 years ± 2.43. This finding contradicts results from Germany (Dorsch *et al*., 2015) where cats diagnosed with FLUTD were older (9.9 years ± 5.09), however it is in agreement with findings from Thailand (Piyarungsri *et al*., 2020) where the mean age record was 3.95 years ± 2.33. This can be attributed to the fact that Malaysia and Thailand have similar climates, geographic location and management styles as compared to Germany. In this study, the majority of cats belonged to multi-cat households, which is a common trend in Malaysia (Alashraf *et al*., 2019; Sivagurunathan *et al*., 2018) and Thailand (Piyarungsri *et al*., 2020) but not in Germany (Dorsch *et al*., 2014). A higher proportion of the patients were managed completely indoors (73.8%). A consequence of multicat – indoor management style is facilities like food water and litter trays are shared amongst indoor cats. Litter tray hygiene and cleanliness in such households has been reported to affect the cats' urination pattern (Ellis *et al*., 2017). This can result in cats withholding urine, avoiding usage of litter trays to avoid encounters with other cats (Cameron *et al*., 2004). Combination of these factors can cause FLUTD amongst this population.

Most of the cats diagnosed with FLUTD in this study were males (85.2%) with females accounting for only 14.7% of cases, which is similar to the findings by Dorsch *et al*. (2015). The domestic short-haired cat is one of the leading cat breeds in Malaysia and it was overrepresented in this study, making the identification of a breed predisposition not possible.

A mean rectal temperature of 37.8 °C ± 1.1 (range 33.4 to 39.3 °C) was recorded. Hypothermia, a common finding in this study, was most likely caused by circulatory shock and accumulation of uraemic toxins. Physical examination revealed that 26 (42.6%) cats had a non-compressible bladder, which is common in those with urinary obstructions along with stranguria and inappetence. Even though 78.7% were presented with stranguria, urethral plugs were found in nine cats (34.6%). Urethral spasms might also cause stranguria and obstruction but evidence to support this event is currently lacking (Osborne C A *et al*., 2000). Obstructions can be life-threatening due to the systemic changes they cause and the possibility of bladder rupture. Urinary bladder bleeding might be responsible for the high rate of haematuria (45.9%) found in this study. Haematuria mainly results from inflammation, high pressure within the bladder and is less often due to previous cystocentesis and catheterisation attempts.

The common haematology findings in this study: neutrophilia with left shift and monocytosis, are non-specific results seen in ongoing infections, combined with chronic inflammation or stress. The back pressure caused by the obstruction impairs glomerular filtration, tubular function and renal blood flow (Klahr *et al*., 1988). This is reflected in the results as hyperkalaemia, uraemia, elevated creatinine and hyperphosphatemia.

Microscopic haematuria was found in most cases of UTI in the present study. Haematuria has been associated with local tissue damage or inflammation, which is common in FLUTD (Alleman & Wamsley, 2017). A higher proportion (75.5%) of the cases recorded a low urine SG, which might be due to the inability of the kidneys to concentrate urine caused by back pressure and possible obstructions. Low urine SG has also been reported in cases of bacterial UTIs (Litster *et al*., 2009). Meanwhile, proteinuria reported in 85% of cases can be due to post-renal factors such as inflammation, haemorrhage and infection. Another important urinalysis result was pyuria, which was present in 58.2% of cases. The result suggests an infection possibly caused by a bacterium. Likewise, urinary bacteria might play a role in the alkaline urine reported in 15 (28.3%) cases, however, urine pH was evaluated using a urine dipstick test. Other methods like a mobile pH meter could be used to get a more accurate reading. Multiple factors can affect urine pH like diet, quality and quantity of water consumption, sample handling and processing time (Albasan *et al*., 2003; Skoch *et al*., 1991; Sturgess *et al*., 2001) .

Plain radiography, contrast study and/or fluoroscopy led to the diagnosis of uroliths, emphysematous cystitis, narrowing or blockage of the urethra and bladder leakage. This enabled clinicians to determine the course of treatment, either surgical or medical management. Bladder rupture is considered an emergency and requires immediate intervention, making its diagnosis crucial and time-sensitive. Ultrasonography revealed a thickened bladder wall leading to a diagnosis of cystitis. Normal cat urine is anechoic, echogenic debris is seen due to the presence of crystals, cells, proteins, cellular debris, calculi or fat droplets. Such sediments were recorded in 31.1% of the cases. Hyperechoic structures like blood clots or membranes were seen within the bladder lumen in 38.3% of the samples. These hyperechoic structures can often block the urine outflow and require regular monitoring.

Out of the 32 (50.8%) culture-positive urine samples, 15 (24.6%) specimens tested positive for a single colony while 17 (27.8%) had multiple colonies. This proportion is higher than previous studies that reported growth of multiple isolates in 14 to 22% of urine samples (Litster *et al*., 2007, 2009; Martinez-Ruzafa *et al*., 2012). Identification of more than one isolate has been linked to contamination due to inadequate sampling, poor handling or storage of urine, rather than an infection with more than one type of bacteria. In this study, most of the samples with more than one isolate were collected by cystocentesis (73.3%; 11/15), thereby reducing the risk of sample contamination during collection. Of the positive urine cultures, 17 (53.1%) were found in cats suffering from their first episodes of FLUTD while 32.2% (10/31) and 16.1% (5/31) were found in second- and third or more-episode cases, respectively. These findings differ significantly from recent reports where 91.2% of positive urine cultures were first-episode cases, 5.3% in second episode cases and only 3.5% in third or more episode cases (Dorsch *et al*., 2014). This could be caused by prior antibiotic treatment for the same or unrelated conditions or antibiotic treatment prior to collection of urine samples. Based on the present results, the first episode of FLUTD cases needs to undergo urine culture testing as part of their diagnostic workup. Furthermore, enforcing that a diagnosis of FIC is made only by exclusion, only after no other cause can be identified.

Staphylococcus species was the leading bacteria isolated in this study at 23.2% with high sensitivity towards amoxicillin/clavulanic acid (80%) and cephalexin (100%). Previous reports showed an increasing trend in the prevalence of *Staphylococcus* species from 7.8% in 1995 to 22.9% in 2014 (Bailiff *et al*., 2008; Dorsch *et al*., 2015; Lund *et al*., 2014; Marques *et al*., 2016; Martinez-Ruzafa *et al*., 2012; Teichmann-Knorrn *et al*., 2018). This increasing trend in *Staphyloccus* spp. could be due to the increase in antibiotic resistance or the development of multidrug resistant strains within the *Staphylococcus* spp.

S. pseudintermedius inhabits the skin of pets but it is capable of causing infections in the animals (Jee *et al*., 2007; Kmieciak & Szewczyk, 2019; Międzobrodzki *et al*., 2010; van Duijkeren *et al*., 2011). Moreover, *S. pseudintermedius* has been isolated from humans in close contact with animals (Boost *et al*., 2011, Savini *et al*., 2014), thereby presenting a zoonotic risk, especially in indoor-managed cats where the owners are in close proximity and handle soiled litter. Although multiple antibiotics are currently effective against *Staphylococcus* species, this could change in the future as seen with other multidrug-resistant *Staphylococcus* species. Early diagnosis is pertinent for the effective treatment of cats with *Staphylococcus* species. Additionally, effective UTI therapy and prudent antibiotic usage are crucial to prevent the development and spread of possible resistance.

E. faecalis was the second most common species isolated with 17.9%, of positive cultures. Previously reported prevalence varied from 6.5 to 43% (Litster *et al*., 2007, 2009; White *et al*., 2016). *Enterococcus* species were once considered commensal organisms of the gut flora with little clinical significance. In this study, they were also found as the leading bacteria isolated in mixed cultures. Previous studies considered *Enterococcus* species as an incidental finding in dog and cat urine due to its presence in mixed cultures (Hall *et al*., 2013; Marques *et al*., 2016). Moreover, it is often isolated using sterile urine collection methods from animals without any clinical signs of UTI (KuKanich & Lubbers, 2015). A high level of fluoroquinolone resistance was found in this study, which might be due to its intrinsic resistance to various groups of antibiotics (Hollenbeck & Rice, 2012). When treating mixed cultures containing *Enterococcus* species, treatment should be aimed at the other bacterial species. This often results in the clearance of *Enterococcus* without targeting therapy at the species (Papich, 2013; Weese *et al*., 2011). However, treatment is based on antimicrobial susceptibility results in cases of infections with only *Enterococcus* species. Pomba *et al*. (2010), reported that chloramphenicol, vancomycin, nitrofurantoin, streptomycin and gentamycin are effective against *Enterococcus* species (Pomba *et al*., 2010).

E. coli accounted for 16.1% of the total positive cultures, lower than previous records of 37% to 71% of feline UTI cases (Bailiff *et al*., 2008; Litster *et al*., 2007; Martinez-Ruzafa *et al*., 2012; White *et al*., 2016). *E. coli* has been reported as the most important infectious cause of UTIs in humans, cats and dogs (Foxman, 2002; Kass, 2002; Russo & Johnson, 2003). The sensitivity of *E. coli* to amoxicillin/clavulanic acid recorded in this study was only 20%, which is lower than multiple earlier reports of sensitivity ranging from 82% to 89% (Bailiff *et al*., 2008; Litster *et al*., 2007, 2009; Mayer-Roenne *et al*., 2007). Antibiotic-resistant forms of uropathogenic *E. coli* (UPEC) have been documented previously in the USA and the UK (Cohn *et al*., 2003; Manges *et al*., 2001; Mulvey *et al*., 2001). *E. coli* is also responsible for relapse or persistence of UTIs for periods of a year or more in cats (Freitag *et al*., 2006), thus highlighting the challenge faced by veterinarians in managing such infections. Given the findings in this study, resistance patterns among *E. coli* isolate in Malaysia should be monitored.

Most human uropathogenic bacteria originate from the gut (Flores-Mireles *et al*., 2015; Magruder *et al*., 2019). This event was supported in this study as the leading bacteria, *Enterococcus* and *Escherichia* species, are also part of the normal feline gut flora. A study conducted in humans with UTIs found that the abundance of *Enterococcus* and *Escherichia* species in the gut was associated with the development of respective bacteriuria (Magruder *et al*., 2019). The intrinsic resistance of *Enterococcus* species to beta-lactams allows it to grow and expand following the depletion of other gut bacteria by antibiotics, resulting in an abundance of *Enterococcus* species in humans treated with beta-lactams (Magruder *et al*., 2019). A similar trend is suggested given the increasing levels of UTIs seen in the feline population along with indiscriminate use of antibiotics. Investigation into the abundance of feline gut bacteria and bacteriuria could support gut microbiota – UTI axis. Modulating this gut microbiota – UTI axis might have the potential of preventing UTIs in the future.

A positive urine culture is necessary to warrant the use of antibiotics (Weese *et al*., 2019) but this is not always practised. Empirical choices vary based on local antibiograms. Guidelines suggest the use of amoxicillin or amoxicillin/clavulanic acid for 3-5 days (Weese *et al*., 2019). In Malaysia, this practice is followed widely where cats are treated with amoxicillin/clavulanic acid while awaiting urine culture results. The antibiotic of choice should be re-assessed once urine culture sensitivity results are available. Other commonly used antibiotics for bacterial cystitis include cephalexin, enrofloxacin and marbofloxacin (Weese *et al*., 2019).

A positive urine culture does not always warrant the use of antibiotics (Weese *et al*., 2019). For instance, the use of antibiotics is not recommended in cases of subclinical bacteriuria, where the animal shows no clinical signs but has a positive urine culture result (Weese *et al*., 2019). Impact factors reported in this study were 30.83 for amoxicillin/clavulanic acid and 31.14 for cephalexin. Prior data is lacking for the impact factor of antibiotics used for FLUTD treatment in Malaysia. Hence, this study provides a baseline for further investigation and monitoring of resistance levels in Malaysia.

Antimicrobial resistance (AMR) is a consequence of indiscriminate uses of antimicrobials, resulting in the development of drug-resistant mutants. As seen in this study, all cats were treated with antibiotics, irrespective of their urine culture results. *E. coli* and *Klebsiella* species reported multidrug resistance.

This study represents primary and referral cases seen in a veterinary hospital. It can be assumed that prior antibiotic treatment influenced the amount of antibiotic resistance and thus on the impact factors. Antibiotics were prescribed for all the cases reported in this study irrespective of their urine culture results. Although the choice of antibiotics was in accordance with international guidelines, the need for administration should be questioned. Antibiotics should be reserved only for patients with positive urine cultures, showing a few urinary clinical signs. Treatment with analgesics and withholding antibiotic treatment pending urine culture results is a reasonable practice (Weese *et al*., 2019) that should be adopted in Malaysia.

This study highlights the increasing presence of bacterial UTIs in the current feline population in Malaysia. Based on the research findings, various levels of antibiotic resistance exist within the country. Culture and sensitivity testing represent the gold standard for choosing appropriate antibiotic therapy and should be performed in all cats presented with FLUTD before antibiotic administration.

In conclusion, the common species of bacteria isolated from feline urine in this study included *Staphylococcus* species, *Enterococcus* species *and Escherichia coli.* Results from this study provide a baseline for impact factors for future monitoring to understand the current trend in Malaysia. Amoxicillin/clavulanic acid and cephalexin displayed the highest impact factors and should be antibiotics of choice while providing empirical treatment. However, initial antibiotic administration should be avoided while awaiting urine culture and susceptibility results. Based on the findings of this study, multidrug resistance patterns were found among *Escherichia coli* and *Klebsiella* species isolates from urine samples in the Malaysian cat population.

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