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Quantitative urinalysis and antimicrobial susceptibility testing of bacterial pathogens in dogs with urinary tract infections

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Abstract
Bacterial urinary tract infection (UTI) is a common clinical condition in dogs and antimicrobial therapy is the cornerstone of its management. Increasing antimicrobial resistance in canine pathogens is of global concern as it increases morbidity, treatment failures and treatment cost. This study identified and quantified the aetiology of urinary tract infections (UTIs) by microbiological culture along with susceptibility testing and quantitative urinalysis in 35 affected dogs. Urine samples were obtained aseptically by cystocentesis from 35 dogs with UTIs. Aerobic urine culture was done by standards methods and bacterial isolates were identified by MALDI TOF. Quantitative urinalysis was done by calculating colony forming units (CFU) per ml of urine and more than 1000 CFU/ml of urine were considered as significant bacteriuria. The antimicrobial susceptibility testing was done using agar disk diffusion method. The 35 urine samples involved in the study on bacteriological evaluation yielded 32 (91.42%) pure culture isolates, whereas three (8.57%) samples indicated mixed growth. Among pure culture, *E. coli* was isolated in 42.85% samples, followed by *Staphylococcus* spp. (25.71%), *Streptococcus* (14.28%), *Proteus-mirabilis* (5.71%), and *Klebsiella* spp. (2.85%). In quantitative urinalysis, *E. coli* had highest CFU/mL of urine (16×10^6) followed by *Streptococcus* spp. (14.9×10^6 CFU/mL), *Staphylococcus* spp. (12.1×10^6 CFU/mL), and least in *Proteus* and *Klebsiella* (10^4 CFU/ml) of urine. Amoxicillin clavulanic acid had the highest sensitivity percentage (74.2%) in dogs with UTIs, followed by ampicillin (62.8%), amoxicillin sulbactam and trimethoprim sulfamethoxazole (60%) each, enrofloxacin and penicillin (51.4%) each, ceftriaxone and gentamycin (45.7%) each, and cefotaxime (40%). *E. coli*, the most prevalent cause of bacterial UTIs had the highest susceptibility to amoxicillin-clavulanic acid.

Keywords: Antimicrobial sensitivity testing, dogs, quantitative urinalysis, urinary tract infection, urine culture

Introduction
The lifetime incidence of UTIs in a dog has been estimated to be 14% [1]. Bacterial urinary tract infections are very often caused by ascending infection from normal skin and gastrointestinal tract flora, which could overcome the normal urinary tract defence mechanisms allowing bacteria, fungi, and viruses to adhere to the uroepithelium and multiply [2]. The bacteria that most commonly causes UTIs include *Escherichia coli, Proteus, Klebsiella, Pasteurella, Pseudomonas*, and *Corynebacterium urealyticum* [3]. UTI is mainly diagnosed by history, physical examination, qualitative and quantitative urinalysis and urine culture tests (the gold standard testing). Urinary tract infections are classified as either simple uncomplicated (a sporadic bacterial infection in an otherwise healthy animal) or complicated (a UTI that occurs in the presence of an anatomic or functional abnormality or a comorbidity that may predispose the patient to persistent infection, recurrent infection, or treatment failure)[4].To establish the presence of bacterial UTI in dogs, cystocentesis is the preferred method for obtaining urine samples aseptically, particularly if a urine culture is intended. Quantitative bacteriological culture remains as the gold standard reference for counting the colony forming units/ml of bacteriuria. Empirical antimicrobial therapy is often initiated for a presumptive diagnosis of UTIs based on the clinical signs and urine culture outcomes by which selection of the first-line empirical therapy could be used to determine the presence of antibiotic-resistant bacteria [4]. Amoxicillin, cephalexin, or trimethoprim-sulfamethoxazole are recommended "first line" antimicrobials for uncomplicated UTIs. Potentiated B-Lactams (amoxicillin-clavulanic acid), fluoroquinolones, or extended-release cephalexin should only be

used for complicated or resistant infections [5]. As a result, the current study aimed to determine the etiological agent(s) responsible for UTI in dogs and their concentrations in urine, as well as their antimicrobial sensitivity pattern in order to establish an appropriate therapeutic protocol.

Materials and Methods

The study was conducted at the Guru Angad Dev Veterinary and Animal Sciences University's Multispecialty Veterinary Hospital in Ludhiana, after taking due approval from Institutional Animal Ethics Committee (IAEC) of the University (GADVASU/2022/IAEC/63/22). A total of 35 dogs presented with clinical signs suggestive of UTIs such as haematuria, stranguria, dysuria, polyuria, polydipsia, depression, weight loss, weakness, dehydration, vomiting, and abdominal pain were selected in the present study. Urine samples were collected via cystocentesis in a sterile plastic container for qualitative and quantitative urinalysis.

Bacterial isolation

Aseptically collected urine samples were inoculated (0.1 ml volumes) on an enrichment media (BHI) Brain Heart Infusion agar using a calibrated platinum loop. Post 24 hours, the plates were incubated aerobically at 37 °C. Subcultures were made from the resulting growth which were isolated for identification of the bacteria, based on Gram's preparation for the morphology, and colony characteristics. *E. coli*, as well as *Klebsiella* spp., were distinguished based on the growth formed on eosin methylene blue agar. A loop full of colonies were mixed with a drop of water on glass slide to see bubbles, indicating catalase test. Large butter like viscid colonies with minimal growth on eosin methylene blue were identified as *Klebsiella* spp., and small shiny colonies with characteristic metallic sheen growth were identified as *E. coli*. The few other organisms were identified via MALDI TOF Biotyper ® Sirius (Bruker 2019, USA) which provided instant readings of the data set down.

Quantitative analysis of urine culture

The gold standard test for diagnosing UTI is by quantitative urine culture testing. Aerobic urine cultures were obtained for each sample wherein, the number of colony forming units/millilitre (CFU/mL) of urine and their bacterial strains involved were determined. Positive samples had at least 100 CFU/ml. Urine cultures (n=35) were isolated and identified via MALDI TOF, and a small sample of the growth was placed in a BHI broth, incubated overnight. 9 micro centrifuge tubes (MCTs) were taken and a 900 µl pipette was used to draw normal saline for turbidity, which was then added to the 9 MCTs. A 100 µl pipette was then used to draw the turbid liquid from the broth, which was then added to the MCTs to perform serial dilution. To maintain the same dilution rate, the remnant from the final tube (9^{th} MCT) was discarded. After which, 9 agar plates (BHI) or any selective medium were taken for the solution to be poured uniformly. The plates were incubated for 24 hours in order to count the colonies. Colonies were counted by placing the plate on the colony counter machine, and CFU/ml were calculated and verified using reference values. The reference standard was cystocentesis specimens, and a cut off of ≥1000 CFU/ml was used to determine significant bacteriuria.

Antibiotic Sensitivity Testing

Antibiotic sensitivity testing was performed on numerous strains of diverse organisms isolated from urine samples of affected animals. Post incubation of the bacterial isolate produced; the turbid broth was directly poured into 9 agar plates spread evenly by smearing over the surface of the agar plates. The antimicrobial discs were placed on the agar gently with centres 30 mm apart and these were then incubated at 37 °C for 24 h. The antimicrobial sensitivity was observed on the basis of zone size interpretation chart. The different antimicrobials used were amoxicillin-clavulanic acid (30 mcg), enrofloxacin (10 mcg), amoxicillin sulbactam (25 mcg) ampicillin (25 mcg), ceftriaxone (10 mcg), cefotaxime (30 mcg), gentamicin (30 mcg) and penicillin-G (10 units). The zones with complete inhibition were measured with calibrated equipment or zone scales, and the sizes were recorded to the nearest mm. (HiMedia Laboratories).

Results

A total of thirty-five urine samples were subjected for bacteriological culture examination and 32 (91.42%) isolates yielded pure culture whereas, mixed growth was observed in 3 (8.57%) samples. Of the pure culture, *E. coli* was found to be the most prevalent and were isolated in 15 (42.85%) samples followed by *Staphylococcus* spp., in 9 (25.71%), *Streptococcus* spp., in 5 (14.28%), *Proteus-Mirabilis* in 2 (5.71%) and *Klebsiella* spp., in 1 (2.85%) sample (Table 1).

Table 1: Organisms isolated from urine samples of dogs suffering from urinary tract infection (n=35)

Sr. No.	Bacterial isolates	No. of samples positive	Percent positivity
1.	*Streptococcus* spp.,	5	14.28%
	Streptococcus agalactiea	3/5	(60%)
	Streptococcus dysgalactiae	2/5	(40%)
2.	*E. coli*	15	42.85%
3.	*Staphylococcus* spp.,	9	25.71%
	Staphylococcus aureus	2/9	(22.22%)
	Staphylococcus schleiferi	2/9	(22.22%)
	Staphylococcus chromogenes	3/9	(33.33%)
	Staphylococcus pseudintermedius	2/9	(22.22%)
4.	*Klebsiella. Pneumoniae*	1	(2.85%)
5.	*Proteus-mirabilis*	2	5.71%
6.	Mixed infections	3	8.57%
	Streptococcus spp., + *E. coli*	1/3	(33.33%)
	Staphylococcus spp., + *E. coli*	1/3	(33.33%)
	Staphylococcus spp.,+ *Streptococcus* spp.,	1/3	(33.33%)

The quantitative analysis of urine culture is shown in table 2. It was found that the predominant bacteria *E. coli* had highest 16×10^6 CFU/ml of urine followed by *Staphylococcus* (12.1×10^6 CFU/ml) and *Streptococcus* (14.9×10^6 CFU/mL). These bacteria were also present in the mixed infection with the concentration 10^6 CFU/ml of urine. The presence of *Proteus* and *Klebsiella* were low and their concentration in the urine was also found to be low (10^4) compared to the predominant bacteria such as *E. coli*, *Staphylococcus* spp. and *Streptococcus* i.e. (10^6).

Table 2: Quantitative analysis of Urine Culture (n=35)

Bacteria Isolated	No of animals affected	Percent (%) Animal affected	Avg No. of Colonies/plate	Total CFU/ml counted	Reference value (Bartges 2004)
E. coli	15	42.8%	160	16×10^6	$\leq 1\times10^3$ (cystocentesis)
Staphylococcus spp.	9	26%	121	12.1×10^6	
Streptococcus spp.	5	14.2%	149	14.9×10^6	
Mixed spp.	3	8.5%	90	9×10^6	
Proteus spp.	2	5.7%	80	8×10^4	
Klebsiella spp.	1	2.8%	77	7×10^4	

The overall antibiotic sensitivity pattern of dogs affected with UTIs are shown in table 3.The overall antibiotic sensitivity pattern of dogs affected with UTIs, showed the highest sensitivity percentage of (74.2%) in amoxicillin clavulanic acid, followed by ampicillin (62.8%), amoxicillin sulbactam and trimethoprim sulfamethoxazole (60%) each, enrofloxacin and penicillin (51.4% each), ceftriaxone and gentamycin (45.7%) each and cefotaxime (40%).

Table 3: Overall Antibiotic Sensitivity Pattern of dogs affected with UTI (n=35)

Sr. No	Antimicrobial drugs	Sensitivity %
1	Amoxicillin Clavulanic acid (AMC)	(26/35) 74.2%
2	Ampicillin (AMP)	(22/35) 62.8%
3	Amoxicillin Sulbactam (AMS)	(21/35) 60%
4	Trimethoprim sulfamethoxazole (TR)	(21/35) 60%
5	Enrofloxacin (Ex)	(18/35) 51.4%
6	Penicillin (P)	(18/35) 51.4%
7	Gentamycin (GEN)	(16/35) 45.7 %
8	Ceftriaxone (CTR))	(16/35) 45.7 %
9	Cefotaxime (CTX)	(14/35) 40%

The antimicrobial sensitivity testing for individual organism isolated is shown in table 4. The highest sensitivity of *E. coli* was observed towards amoxicillin-clavulanic acid (80%), followed by ampicillin (66.6%), enrofloxacin and amoxicillin sulbactam (60%), penicillin (53.3%), ceftriaxone and trimethoprim-sulfamethoxazole (46.6% each), gentamycin (40%) and cefotaxime (33.3%). Similarly, the highest sensitivity of *Staphylococcus* spp. was towards ceftriaxone and trimethoprim sulfamethoxazole (77.7%) each, followed by amoxicillin sulbactam, gentamycin and penicillin (66.6% each), amoxicillin clavulanic acid, ampicillin and ceftriaxone (55.5% each) and least for enrofloxacin (44.4%). The highest sensitivity of *Streptococcus* spp. was seen in amoxicillin-clavulanic acid, ampicillin, amoxicillin sulbactam and trimethoprim-sulfamethoxazole (80%, each), followed by enrofloxacin, gentamycin, cefotaxime and penicillin (60% each) and the least in ceftriaxone (40%). The highest sensitivity of mixed infection (*Staphylococcus* spp. + *Streptococcus* spp. and *Streptococcus* spp.+ *E. coli*) was 100% towards amoxicillin-clavulanic acid, ampicillin and amoxicillin sulbactam. Also, *Staphylococcus* spp.+ *E. coli* showed sensitivity of (100%) towards enrofloxacin, amoxicillin-clavulanic acid, ampicillin, amoxicillin sulbactam, gentamycin and ceftriaxone.

The highest sensitivity of *Proteus-mirabilis* was towards trimethoprim sulfamethoxazole (100%), followed by amoxicillin-clavulanic acid and ampicillin (50%, each). None of the isolates were found sensitive to the remaining antimicrobials (enrofloxacin, amoxicillin sulbactam, gentamycin, cefotaxime, ceftriaxone and penicillin). The highest sensitivity of *Klebsiella* spp. was towards enrofloxacin, amoxicillin-clavulanic acid, cefotaxime, trimethoprim- sulfamethoxazole and penicillin (100%). None of the isolates were found sensitive to the remaining antimicrobials.

Table 4: Antimicrobial sensitivity testing for individual organism isolated (n=35)

Organisms isolated	Antimicrobial Sensitivity %								
	Ex	AMC	AMP	AMS	GEN	CTR	CTX	TR	P
E. coli	(9/15) 60%	(12/15) 80%	(10/15) 66.6%	(9/15) 60%	(6/15) 40%	(7/15) 46.6%	(5/15) 33.3%	(7/15) 46.6%	(8/15) 53.3%
Staphylococcus spp.	(4/9) 44.4%	(5/9) 55.5%	(5/9) 55.5%	(6/9) 66.6%	(6/9) 66.6%	(7/9) 77.7%	(5/9) 55.5%	(7/9) 77.7%	(6/9) 66.6%
Streptococcus spp.	(3/5) 60%	(4/5) 80%	(4/5) 80%	(4/5) 80%	(3/5) 60%	(2/5) 40%	(3/5) 60%	(4/5) 80%	(3/5) 60%
Staphylococcus spp.+ *E. coli*	(1/1) 100%	(1/1) 100%	(1/1) 100%	(1/1) 100%	(1/1) 100%	(1/1) 100%	(0/1) 0%	(0/1) 0%	(0/1) 0%
Staphylococcus spp. + *Streptococcus* spp.	(0/1) 0%	(1/1) 100%	(1/1) 100%	(1/1) 100%	(0/1) 0%	(0/1) 0%	(0/1) 0%	(0/1) 0%	(0/1) 0%
Streptococcus spp.+ *E. coli*	(0/1) 0%	(1/1) 100%	(1/1) 100%	(1/1) 100%	(0/1) 0%	(0/1) 0%	(0/1) 0%	(0/1) 0%	(0/1) 0%
Proteus-mirabilis	(0/2) 0%	(1/2) 50%	(1/2) 50%	(0/2) 0%	(0/2) 0%	(0/2) 0%	(0/2) 0%	(2/2) 100%	(0/2) 0%
Klebsiella spp.	(1/1) 100%	(1/1) 100%	(0/1) 0%	(0/1) 0%	(0/1) 0%	(0/1) 0%	(1/1) 100%	(1/1) 100%	(1/1) 100%

Discussion

Urinary tract infections are frequently encountered in dogs, and its diagnosis is made on the basis of history, physical examination, thorough qualitative and quantitative urinalysis, and urine culture. Urine culture is regarded the gold standard test for UTI. The UTIs in dogs may be triggered by a wide range of bacteria and can be induced by one or more organisms. The present study showed that UTIs were caused by various organisms of which *E. coli* was the most commonly found pathogen in canine UTIs followed by *Staphylococcus aureus* which is consistent with the findings of other studies [6, 7, 8, 9, 10, 11, 12] but for other isolates results fluctuates. The variation in the bacterial uro-pathogenic prevalence might be due to environmental factors. Additional research is needed to determine if these isolates are gastrointestinal commensals, environmental organisms, or extra intestinal uro-pathogenic *E. coli*.

The benefit of quantitative culture techniques is the ability to identify the amount of bacterial growth (colony counts), which may be used to assess the significance of results. To determine the significant bacteriuria (the number of bacteria per unit volume of urine), quantitative cultures were performed. It has been suggested that any bacterial growth obtained from aseptic samples would be regarded as significant. In this study, all urine samples that were screened positive for bacterial cultures had a bacterial count of 10^4 to 10^6 CFU/ml. It was found that the primary bacteria i.e., *E. coli*, *Staphylococcus* spp., *Streptococcus* spp., isolated in the study were present at a concentration of 10^6. These bacteria were also present in the mixed infection at the concentration of 10^6. The presence of *Proteus* and *Klebsiella* was low and their concentration in the urine was also found to be low 10^4 compared to the predominant bacteria such as *E. coli*, *Staphylococcus*. All urine samples were obtained by cystocentesis in this study, and bacterial cut off counts of more than $>10^3$ were observed, while $>10^4$ to 10^5 indicated significant bacteriuria via urethral catheterization and more than 10^6 as a cut off of voided urine samples, provided the specimens are refrigerated and the bacterial culture is evaluated on the day of collection. Similar findings were reported by Dunning and Stonehewer 2002 [13], Bartges 2004 [14] who concluded that, $>10^3$ CFU/ml was indicative of significant bacteriuria in dogs however, Gatoria *et al.* (2006) [15] on the other hand, discovered that the isolation of more than 10^2 CFU/ml in a urine sample acquired by cystocentesis might be suggestive of UTIs. Few other researchers [2, 4, 16, 17] reported that all urine samples were obtained by cystocentesis and observed bacterial count of more than $>10^4$ and $>10^6$ which indicated significant bacteriuria.

In most cases, antimicrobial therapy is recommended to alleviate patient discomfort while monitoring culture and susceptibility findings. When considering an antibiotic, it is necessary to evaluate the bacterium's susceptibility, potential adverse effects, and issues regarding the prudent use of certain antimicrobials and antimicrobial classes. Overuse of antimicrobial agents, particularly for prophylactic use, to avoid surgical site infections or infections associated with other urogenital conditions, might have resulted in the evolution of resistant strains. The best possible reason the development of resistance by uropathogens to commonly used antibiotics in India might be due to conventional, prolonged, and indiscriminate use of antibiotics in the field conditions. In the current study, using the disc diffusion method, the overall antibiotic sensitivity pattern of dogs affected with UTI, among all bacterial infections, showed the highest sensitivity percentage of (74.2%) in amoxicillin clavulanic acid, followed by ampicillin (62.8%), amoxicillin sulbactam and trimethoprim-sulfamethoxazole (60% each), enrofloxacin and penicillin (51.4% each), ceftriaxone and gentamycin (45.7% each), and cefotaxime (40%). Similar findings were recorded by other researchers [17, 18, 19]. Quantitative urinalysis and antibiotic sensitivity testing are essential tools for prudent use of antibiotics for reducing the emergence of antimicrobial resistance in uropathogens.

Conclusion

The present study indicated that *E. coli and Staphylococcus* spp. with concentration of 10^6/ml of urine are the most prevalent bacterial isolate from UTI affected dogs. Amoxicillin clavulanic acid is the most effective antibiotics for treating UTIs in dogs based on antimicrobial sensitivity testing.

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