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Efficacy of Enrofloxacin in the therapeutic management of bacterial lower urinary tract infection (Cystitis) in geriatric dogs

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Abstract
Out of 134 geriatric dogs diagnosed with bacterial lower urinary tract infection (BLUTI) at veterinary clinical complex, college of veterinary science, Rajendranagar, 20 cases with cystitis that were confirmed by history, clinical symptoms, urinalysis, Haemato-biochemical and biomarker estimations, imaging techniques and cultural studies, were selected for therapeutic studies, by randomly dividing them into two groups *viz*., Group I and II, with 10 dogs in each. Therapeutic regimen for Group I cystitis dogs included Punarnava herbal drug and in Group II an antibiotic, enrofloxacin that have showed highest sensitivity on *in vitro* antibiogram for the isolates (same/ different) of that particular group dogs with cystitis. The efficacy of treatment regimens was assessed on day 15 by recording remission of clinical symptoms, near normalization of abnormal findings of urinalysis, Haemato-biochemical and biomarkers estimations, disappearance of abnormal ultrasonographical findings and microbiological cure by cultural studies after therapy. Alleviation in frequency and severity of the clinical signs was observed from 7th day of therapy among 4 dogs but with complete improvement among 7 dogs by 15th day. Non-significantly reduced haematological parameters like Hb (11.36±0.58 g/dl), TEC (5.36±0.30 X10^{6}/µl) and PCV (37.52 ± 0.44%) of group II dogs showed improvement and reached normalcy by 15th day. Irregular contour of bladder wall surface, sludge, and hyperechoeic debris in the bladder lumen along with thickened urinary bladder wall ranging from 5 mm to 17 mm. Microbiological cure on 15th day of therapy was 70% only in this group of dogs with cystitis.

Keywords: Bacterial lower urinary tract infection, Enrofloxacin, Clinical symptoms, Urinalysis, Culture, geriatric dogs

1. Introduction
Urinary tract infection (UTI) refers to the microbial colonization of the urine or of any urinary tract organ (Greene, 2012) [1]. Urinary tract infection (UTI) of bacterial origin is the most common infectious disease of dogs, affecting 14 percent of all dogs during their lifetime. Most UTIs are the result of ascending bacteria from rectal or fecal contamination or from the distal urogenital tract. The infection is more prevalent in older dogs with a median age of 9 years (Wong *et al.*, 2015) [2]. Bacterial urinary tract infections can be classified as simple or uncomplicated, which is a sporadic bacterial infection of the urinary tract in an otherwise healthy individual with normal urinary tract anatomy and function, and it does not occur more frequently than every 4 to 6 months, and complicated, which is defined as a urinary tract infection (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. Common comorbidities of complicated UTI include diabetes mellitus, chronic kidney disease (CKD), urolithiasis, immune suppression etc. (Wood, 2017) [3]. Urinary tract disease is commonly encountered in dogs and cats and accounts for significant use (and presumably also overuse and misuse) of antimicrobials. Improper therapy can lead to a variety of patient health (e.g., failure to resolve infection), economic (e.g., need for repeated or prolonged treatment), public health (e.g., antimicrobial resistance) and regulatory (e.g., antimicrobial use) concerns. In human medicine, antimicrobial use guidelines such as those developed by the Infectious Diseases Society of America (IDSA) are widely respected and provide excellent guidance to physicians on management of various infectious diseases, including urinary tract infections (UTIs) (Hooper, 2000 and Cohn *et al.*, 2003) [4, 5].

The Enrofloxacin has good bioavailability and penetrate most tissues well, especially bronchial mucosa, lung, gall bladder, kidney, prostate and genital tract. The absorption of the oral version of these drugs is excellent, and thus blood levels achieved with the oral version are similar to those with the intravenous route (Ettinger and Feldman, 2010) [6]. The present study was conducted to ascertain the efficacy of Enrofloxacin in management of bacterial lower urinary tract infection in geriatric dogs.

2. Materials and Methods

Dogs presented to the Veterinary Clinical Complex, College of Veterinary Science., Rajendranagar during the period from January 2021 to April 2022 were considered for the present study. The study comprised of apparently healthy adult dogs and geriatric clinical cases. Ten apparently healthy adult dogs of different breeds were selected as control group for obtaining normal data for comparison of parameters under study. Out of 7280 total adult (> 6 years) dogs, 620 were geriatric, and out of which, 184 dogs that were showing the clinical signs indicative of bacterial lower urinary tract infection (Cystitis), such as haematuria, pollakiuria, stranguria, dysuria, periuria, abdominal pain, foul smelling urine, depression, loss of appetite, anuria and fever etc., were taken up for detailed study. 134 geriatric dogs that were diagnosed with bacterial lower urinary tract infection that were confirmed by history, clinical symptoms, urinalysis, Haemato-biochemical and biomarker estimations, imaging techniques and cultural studies, finally 20 cases with cystitis were selected for therapeutic studies, by randomly dividing them into two groups *viz*., Group I and II, with 10 dogs in each. Group II cystitis dogs treated with Enrofloxacin @ 10 mg/ kg B.W. orally once a day and supportive drugs. The data collected were statistically analyzed as per the methods described by Snedecor and Cochran (1994) [7] by using SPSS package version 20.00. The significance of results was evaluated by applying one-way ANOVA and t-test to determine significant difference among means.

3. Results

The dogs of this group that had cystitis with *Staphylococcus spp.* (3 dogs), *E. coli spp.* (4 dogs), *Proteus spp.* (2 dogs) and *Pseudomonas spp.* (1 dog), were treated with an antibiotic Enrofloxacin @10 mg for kg B.W. orally s.i.d. for 14 days. Supportive medications like analgesic/anti-inflammatory, haemostatic drugs, vitamin- B complex, antiemetics, antacids, proton pump inhibitors, fluid therapy (DNS and RL) and oral haematinics were also given as needed. Almost all the 10 dogs of this group were showing similar signs on day '0' of presentation, that include pollakiuria, haematuria, abdominal pain, stranguria, foul smelling urine and periuria, apart from other general signs like rise in temperature, reduced food intake and weakness. Alleviation in frequency and severity of the clinical signs was observed from 7th day of therapy among 4 dogs but with complete improvement among 7 dogs by 15th day. Where as, the remaining 3/10 refractory dogs were still showing mild to moderate haematuria (1), stranguria (3) and foul odour (3) on day 15. These dogs were treated with tab Punarnava from day 16 and continued for day 30, which showed marked improvement and complete cure by day 30. However, 4/7 recovered dogs showed antibiotic induced gastritis, and anorexia during the treatment period, that were managed with antiemetics, H_2 receptor blockers and proton pump inhibitors. All the dogs of this group were also monitored for 6 months post therapy and during which 2/10 dogs that received antibiotic therapy showed relapse of signs during 3rd month and 1 dog during 5th month. Various abnormal colours of urine samples from affected dogs, *viz*., dark yellow (7 dogs), deep amber (1 dog), brown (1 dog) and reddish (1 dog) was noticed on day 0 (before treatment) in comparison to apparently healthy adult dogs, that was pale yellow. Among these, five dogs showed improvement by 10th day and 2 dogs by 15th day but 3/10 dogs which had deep amber to brown and reddish colour urine did not show any improvement by day 15. However, these dogs subsequently improved and urine colour returned to normal by day 30. The physical appearance of the urine of affected dogs was cloudy (6 dogs) and turbid (2 dogs) but clear in 2 dogs. These abnormalities reached to normal by 15th day among all the affected patients. Similarly, Odour of the urine from affected animals varied from strong ammonical (6 dogs) to bad Odour (4 dogs) that disappeared and reached to normal among 7/10 dogs by 15th day, and among all the affected dogs subsequently, by day 30. The pH of the urine was alkaline among 7/10 dogs that were infected with *Staphylococcus spp*. and *Proteus spp.* which turned to acidic among 5 of the affected dogs by day 15 post treatment and among the remaining 2 by day 30. Other abnormalities noticed on chemical examination of urine samples were proteinuria, pyuria and Haematuria among 4, 3 and 3 dogs, respectively, also showed slight improvement by day 15 and complete remission by day 30. Microscopic examination of urine sediment of dogs with cystitis showed RBC's (+++), WBC's (+++) and epithelial cells (++) on the day of presentation also normal by 15th day among 7 and 30th day among all the affected dogs (Table 1, 2, 3 and fig. 1, 2, 3). The non-significantly reduced haematological parameters like Hb (11.36±0.58 g/dl), TEC (5.36±0.30 X10^6/µl) and PCV (37.52±0.44%) of cystitis-affected dogs showed improvement and reached normalcy by 15th day when compared with pre-therapeutic (0 day) values. Similarly, the elevated mean value of TLC (16.58 ± 0.43 X10^3/µl) also reduced to near normal by 15th day of therapy. Regarding biochemical findings slightly elevated mean creatinine (1.46±0.22 mg/dl) and BUN (26.34±0.20 mg/dl) values has reached to normal values by 15th day. Further, the significant (p<0.05) hypoproteinaemia (4.16±0.26 g/dl) and hypoalbuminaemia (2.14±0.21 g/dl) also improved to near normal values (6.94±0.32 g/dl) and (2.95±0.16 g/dl) respectively, by 15th day. Significantly (p<0.05) elevated mean C-reactive protein (49.3±4.4 mg/L) values improved (25.8±3.2 g/L) by 15th day of therapy and reached to normal reference range (12.4±2.6 g/L) on 30th day of therapy (Table 4 and Fig. 4.). Ultrasonographic findings of the cystitis dogs revealed irregular contour of bladder wall surface, sludge and hyperechoeic debris in the bladder lumen along with thickened urinary bladder wall ranging from 5 mm to 17 mm. These abnormal ultrasonographic changes disappeared and the mean bladder wall thickness (16.42 + 1.48) among the affected dogs of this group that was significantly (p<0.05) increased on day 0 when compared to apparently healthy adult dogs (1.92+0.25) has reduced to 15.54 + 1.28 mm on day 15 that was non-significant; However, subsequent evaluation showed a non- significant decreased values of 14.52 + 0.75 on day 30 and significant (p<0.05) decreased values of 12.46+0.68 on day 60. Among the ten dogs with bacterial cystitis, three dogs showed positive culture i.e., *staphylococcus spp*. (2 dogs) and *E. coli* (1 dog) on 15th day, but following treatment with Punarnava from day 16, these refractory samples also showed negative culture on day 30. Thus, the antibiotic Enrofloxacin is also effective in treatment of bacterial cystitis but with 70% microbial cure among the dogs of the present study.

Table 1: Physical examination of urine samples in group II dogs before and after therapy

Sl. No.	Parameter	Apparently healthy adult animals	Dogs with cystitis	Group II (n=10)		
				Day "0"	Day "15"	Day "30"
1	Colour	Pale yellow	Dark yellow	7	0	0
			amber	1	1	0
			Brown	1	1	0
			Reddish	1	1	0
2	Transparency	Clear	Cloudy	6	0	0
			Turbid	2	0	0
3	Odour	Slight ammonical	Strong	6	3	0
			Bad	4	0	0

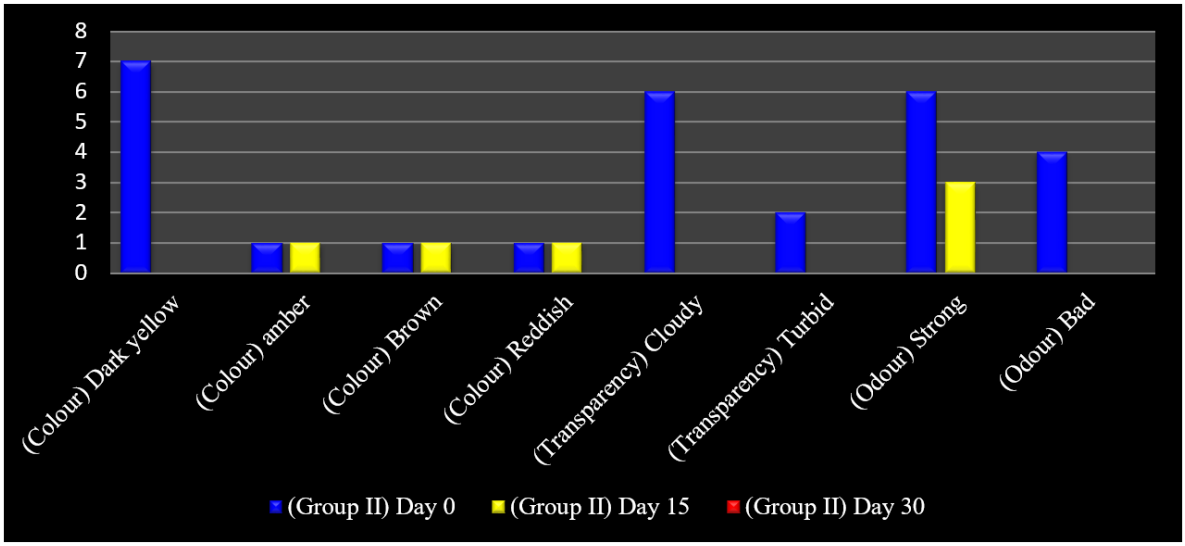

Fig 1: Physical examination of urine samples in group II dogs before and after therapy

Table 2: Chemical examination of urine samples by dip stick analysis in group II dogs before and after therapy

Sl. No.	Parameters	Severity level	Apparently healthy adult animals	Group II (n=10)		
				Day "0"	Day "15"	Day "30"
1	pH	Acidic (<7)	Acidic	3	8	10
		Alkaline (≥7)	-	7	2	0
2	Leukocytes	Mild	Absent	0	0	0
		Moderate	Absent	3	0	0
		Severe	Absent	0	0	0
3	Blood	Mild	Absent	0	0	0
		Moderate	Absent	0	0	0
		Severe	Absent	3	0	0
4	Bilirubin	Mild	Absent	0	2	2
		Moderate	Absent	3	0	0
		Severe	Absent	0	0	0
5	Ketone bodies	Mild	Absent	0	0	0
		Moderate	Absent	0	0	0
		Severe	Absent	0	0	0
6	Urobillinogen	Mild	Present	4	4	5
		Moderate	Present	0	1	0
		Severe	Present	0	0	0
7	Glucose	Mild	Absent	0	0	0
		Moderate	Absent	0	0	0
		Severe	Absent	0	0	0
8	Protein	Mild	Absent	0	0	0
		Moderate	Absent	0	3	0
		Severe	Absent	4	0	0

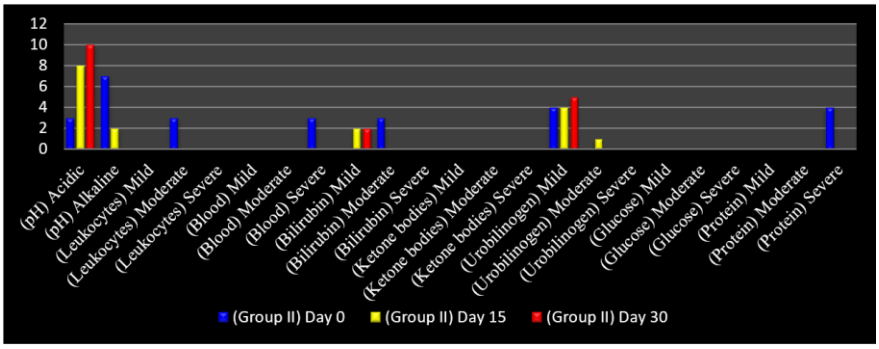

Fig 2: Chemical examination of urine samples in group II dogs before and after therapy

Table 3: Microscopic examination of urine sediment in group II dogs before and after therapy

Microscopic findings		Apparently healthy adult animals	Group II (n=10)		
			Day "0"	Day "15"	Day "30"
RBC		1 cell/hpf	7	3	0
WBC		1 cell/hpf	6	3	0
Epithelial cells		1- 2 cells/hpf	5	3	0
Casts		Absent	0	0	0
Bacteria		Absent	2	1	0
Crystals	Struvite	0	0	0	0
	Calcium oxalate	0	0	0	0
	Bilirubin	0	0	0	0

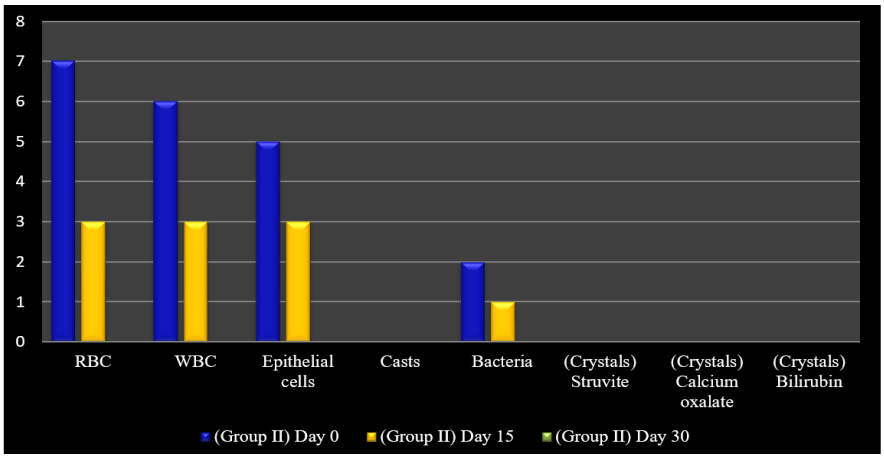

Fig 3: Microscopic examination of urine sediment in group II dogs before and after therapy

Table 4: Haemato- biochemical and biomarker findings in Group-II dogs before and after therapy (Mean ± SE)

Sl. No.	Parameter	Apparently healthy adult dogs (n = 10)	Dogs with Cystitis (n = 10) '0' day	15th day (post-therapy)	30th day (post-therapy)
1.	Hb (g/dl)	13.44±0.30	11.36±0.58	13.02±0.41	13.46±0.35
2.	PCV (%)	42.31±0.34	37.52 ± 0.44	40.76±0.38	42.30±0.56
3.	TEC ($X10^6$/µl)	6.42±0.23	5.36±0.30	6.12±0.21	6.44±0.27
4.	TLC (X 10^3 /µl)	9.76± 0.34	16.58±0.43*	11.94±0.37	9.72± 0.35
5.	Neutrophils (%)	70.44±0.35	79.26±0.51*	72.44±0.46	69.76±0.38
6.	Lymphocytes (%)	21.67±0.46	18.64±0.41	20.68±0.29	22.94±0.24
7.	Eosinophils (%)	3.64±0.24	3.82±0.22	3.66±0.25	3.56±0.26
8.	Monocytes (%)	2.56±0.16	2.74±0.18	2.58±0.14	2.52±0.24
9.	Basophils (%)	0.62±0.15	0.83±0.15	0.63±0.17	0.61±0.14
10.	Platelets (X 10^3 /µl)	264.21±12.5	232.45±4.6	258.21±5.1	262.37±4.3
11.	Creatinine (mg/dl)	1.25±0.13	1.46±0.22	1.26±0.12	1.22±0.16
12.	BUN (mg/dl)	22.14±0.13	26.34±0.20	21.65±0.28	20.24±0.17
13.	ALT(IU/L)	38.29±1.11	48.32±1.12	43.36±1.16	40.85±1.08
14.	Total Protein(g/dl)	7.21±0.22	4.16±0.26*	6.94±0.32	7.18±0.23
15.	Albumin (g/dl)	3.40±0.18	2.14±0.21*	2.95±0.16	3.42±022
16.	Glucose (mg/dl)	80.11±1.73	76.65±1.24	81.41±1.18	83.81±1.32
17	SDMA (µg/dl)	8.15±0.21	8.62±0.16	8.43±0.22	8.46±0.24
18	C-reactive protein (CRP) (mg/L)	10.2±2.6	49.3±4.4*	25.8±3.2**	12.4±2.6

*: Significant at when compared to apparently healthy adult dogs ($p<0.05$)
**: Significant at when compared to '0' day ($p<0.05$)

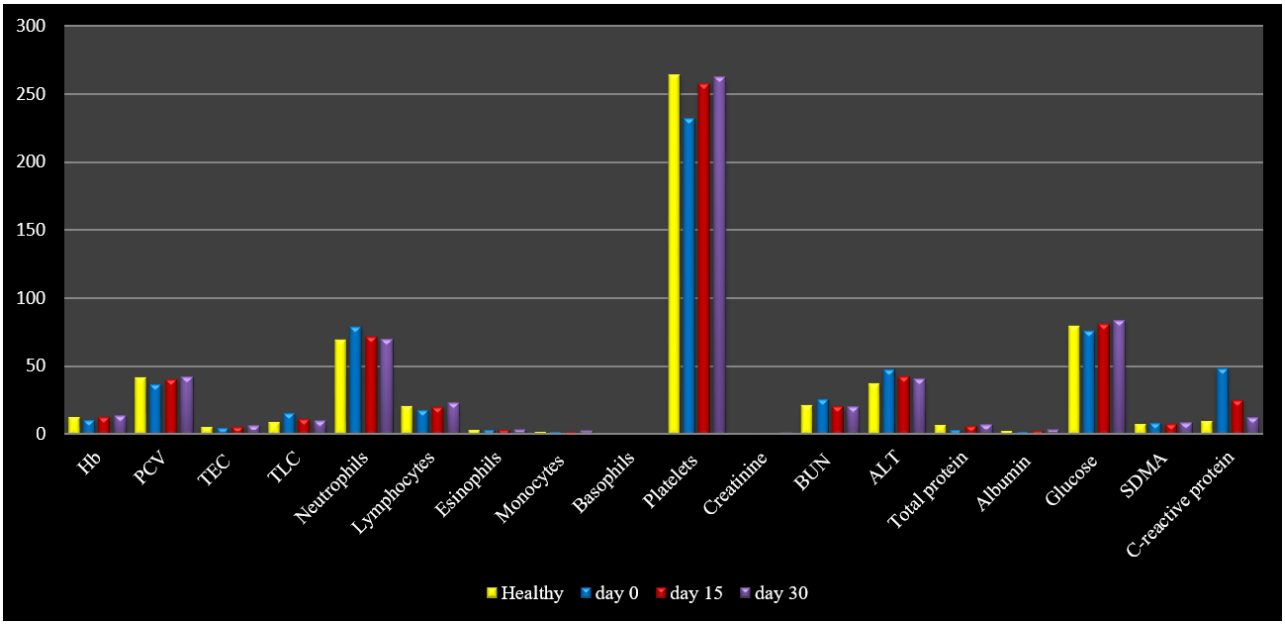

Fig 4: Haemato-biochemical and biomarker findings in Group-II dogs before and after therapy.

4. Discussion

The most common clinical signs of enrofloxacin treated cystitis affected dogs showed improvement from 7th day of therapy among 4 dogs but with complete improvement among 7/10 dogs by 15th day. Where as, the remaining 3/10 refractory dogs also showed marked improvement and complete cure by day 30 when treated with punarnava. Further, 4/7 recovered dogs showed antibiotic induced gastritis, and anorexia during the treatment period, that were managed with antiemetics, H_2 receptor blockers and proton pump inhibitors. All these dogs were also monitored for 6 months post-therapy and during which 2/10 dogs that received antibiotic therapy showed relapse of signs during 3rd month and 1 dog during 5th month. Other abnormalities of urine, and Haemato-biochemical parameters were also shown improvement in 7/10 dogs by day 15, that were also completely recovered following 15 days medication of punarnava. Similarly chemical parameters, cytology and microbiological abnormalities also improved in only 7 dogs by the end of treatment period. Further, the microbiological cure was also noticed as culture negative among the refractory cases on day 30. Thus based on clinical cure and microbiological cure by 15th day post therapy among the dogs of present study, enrofloxacin was effective in only 70 percent of the affected dogs. The findings of the present study are in agreement with Westdropp *et al*. (2012) [8] who observed clinical and microbiological cure rates as 88.6 percent and 94.3 percent respectively. Raz *et al.* (1989) [9] documented 89 percent clinical cure rate and 81.1 percent microbiological cure rate with Ciprofloxacin among the dogs with UTI. Westropp *et al.* (2012) [8], who found fluoroquinolones to be effective in dogs with UTI. Oluoch *et al*. (2001) [10] stated that fluoroquinolones were often used to treat UTIs because of their bactericidal property with high urine concentrations, effective against most of the uropathogens and penetrate the urinary tract tissues. Enrofloxacin accumulates to particularly high concentrations within the urinary tract and, is efficacious against a spectrum of uropathogens. Enrofloxacin is an antimicrobial agent commonly used in veterinary medicine to treat urinary tract infections (Ettinger and Feldman, 2010 and Westropp *et al.*, 2012) [6, 8]. Enrofloxacin, that belongs to the fluoroquinolones group, more specifically the 6-fluoro-7-piperazinyl-4-quinolones. This broad-spectrum antibiotic is widely used in veterinary medicine as an antibacterial agent, showing high activity against both Gram-negative and Gram-positive bacteria. Enrofloxacin is highly lipophilic. The quinolones are unique among antimicrobial agents in that they target bacterial topoisomerases.' Topoisomerases maintain cellular DNA in an appropriate state of supercoiling in both replicating and non-replicating regions of the bacterial chromosome. Four types of topoisomerases exist. The quinolones target DNA gyrase (also termed "topoisomerase type II") and topoisomerase IV (types I and III are not targets of the quinolones). DNA gyrase removes the excess positive supercoiling that builds up ahead of the DNA replication fork as a result of enzymes replicating DNA. Without DNA gyrase-mediated relaxation, this excess positive supercoiling would ultimately arrest DNA replication. After DNA replication, topoisomerase IV activity helps to separate the daughter DNA molecules. When the quinolones target DNA gyrase, the complex between DNA and DNA gyrase is stabilized. A hypothesis is that the replicating fork then collides with this complex, an outcome leading to a sudden and lethal cessation of DNA replication. Quinolone targeting of topoisomerase IV may also arrest the DNA replication, but in a different way that is, by blocking this enzyme's normal function of decatenation of linked daughter DNA molecules. The activity of the quinolones against gram-positive bacteria, such as Staphylococcus aureus, streptococcus, may primarily be the result of targeting topoisomerase IV. Conversely, the activity of the quinolones against gram-negative bacteria such as *E. coli*, *Pseudomonas*, *proteus* and *klebsiella* may primarily be the result of targeting DNA gyrase (Neuman, 1986; Kaatz and Seo, 1997; Gootz and Brighty, 1998; Polzin 1999; Wright *et al.*, 2000; Ettinger and Feldman, 2010 and Colakoglu *et al.*, 2017) [11, 12, 13, 14, 15, 6, 16]. The fluoroquinolones are well tolerated with fewer adverse effects that are not very serious, especially when compared to their benefits. The most common side effects of enrofloxacin are digestive disorders including nausea, abdominal discomfort, vomiting, diarrhea and lack of appetite. Rarely, uncoordinated walking, seizures, depression, lethargy and allergic reactions (Gootz and Brlghty, 1998; Walker, 1999; Ettinger and Feldman, 2010; Westropp *et al.*, 2012 and Punia *et al.*, 2018) [13, 17, 6, 7, 18].

5. Conclusion

Enrofloxacin accumulates in the urinary tract at higher concentrations and is efficacious against a spectrum of uropathogens, but in our study based on microbiological cure by 15th day post therapy among the dogs affected with cystitis, Enrofloxacin was effective in only 70 percent.

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