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The Effect of Cefovecin Sodium in Shelter Dogs with Bacterial Lower Respiratory Disease

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HIGHLIGHTS

- Bacterial respiratory disease can occur in shelter dogs on occasion.
- Empirical antimicrobial drug selection may be performed based on etiologic consideration.
- Cefovecin sodium seems suitable for the empirical treatment of shelter dogs.
- Cefovecin should only be used on a case-by-case basis.

Abstract: This study evaluated the clinical and bacteriological efficacy of cefovecin sodium in shelter dogs with bacterial lower respiratory disease. All dogs (n = 32) with lower respiratory disease were divided into two treatment groups: the cefovecin (n = 16) and the ceftriaxone (n = 16) groups. On the first five days and the 8th day of treatment, and after treatment (15th day), the examination of all dogs was performed. Blood analysis and thoracic radiographic imaging were done. In bronchoalveolar lavage fluids, in the cefovecin group, *Bordetella bronchiseptica* (n=13), *Staphylococcus* spp. (n=9), *Streptococcus* spp. (n=7), *Klebsiella pneumonia* (n=1); in the ceftriaxone group; *B. bronchiseptica* (n=5), *Escherichia coli* (n=5), *Pasteurella canis* (n=4), *Streptococcus* spp. (n=3), *Staphylococcus aureus* (n=1), *Pasteurella aerogenes* (n=1) and *Klebsiella oxytoca* (n=1) were isolated and identified. Cefovecin and ceftriaxone sodium treatment protocols had anti-bacterial efficacies of 68.75% and 100%, respectively. In light of the study results, it is concluded that although cefovecin sodium looks to be an antibacterial drug that may be used to treat bacterial lower respiratory tract infections in shelter dogs due to its ease of use, cefovecin and other cephalosporins should not be used empirically as they may contribute to bacterial resistance.

Keywords: Bacterial lower respiratory infection; cefovecin; clinical efficacy; empirically treatment; shelter dog.

INTRODUCTION

Even though the primary causative agents are viruses, bacteria are also causative agents secondary to viruses in the aetiology of respiratory diseases in dogs [1–3]. The prevalence of infectious respiratory diseases, especially in environments where the dogs are densely hosted, such as temporary animal shelters and research centres, is quite high and can progress to severe outbreaks [4,5].

The most common among respiratory diseases in dogs housed in shelters is canine infectious respiratory disease [6]. This disease, also known as the Kennel Cough Complex, common in dogs rehabilitated in crowded environments is a complex respiratory disease that can progress with anorexia, depression, vomiting, fever, dry cough, tracheal sensitivity and nasal discharge [5,7–9]. One or more microorganisms other than viral agents are effective in the aetiology of the disease [8,9]. Although viral agents are the primary factors in the pathology of the disease [3], since secondary bacterial agents accompany them at this stage, bacteria may be a serious problem in the treatment of this disease [8]. Bacterial agents such as *Bordetella bronchiseptica*, *Mycoplasma* spp., *Escherichia coli*, *Pseudomonas* spp., *Pasteurella* spp., and *Streptococcus equi* subsp. *zooepidemicus* may have a causative role in shelter dogs suffering respiratory disease [6,10].

Although respiratory diseases of dogs and cats can be presumptively diagnosed based on physical examination and historical findings, for a more accurate approach to respiratory tract diseases, auxiliary diagnostic methods are also needed [11]. Radiographic examination is an important tool used in the diagnosis of thoracic diseases and pathologies in small animal practice [12–15].

Bacterial cultures and cytological examinations of bronchopulmonary secretions can also be helpful for the diagnosis of lower respiratory tract diseases (LRTD) [11,13,16,17]. It has been suggested in many different studies that cytological and bacterial analyses of bronchoalveolar lavage fluid (BAL) are important in the detection of LRTD [2,16,17]. Based on bacterial culture results, antibacterial treatment is more effective [2,13,18]. But, in the cases where these tests cannot be applied, if antibacterial drugs are to be preferred, they should be chosen according to epidemiological information about the target bacteria at local or regional level [19]. It is reported that respiratory disease is the third most common reason for antibiotic prescriptions in dogs, and among these antibiotics, cefovecin and amoxicillin-clavulanate are the most preferred drugs for this disease [20–22]. Cefovecin is a new, semi-synthetic, long-acting third generation cephalosporin [23] licensed for use in many countries in the European Union, New Zealand, South America, and Asia [24]. Gram-negative organisms that include *E. coli*, *Pasteurella multocida*, *Proteus* spp., *Klebsiella* spp. (including *Klebsiella pneumoniae*), and *Enterobacter* spp., on which cefovecin acts well [23,25], are often isolated from dogs with LRTD [2,6,10,12,26]. It is emphasized that cefovecin might be used in respiratory diseases [19,27], but its possible contribution to antibiotic resistance should also be taken into account [19,21,27].

In this study, considering its use in skin [28], dental [29] and anaerobic infections [25], it was hypothesized that cefovecin, recommended for the treatment of urinary system infections in dogs due to its efficacy and ease of use [30], may also be used in bacterial lower respiratory tract disease, which is common in shelter dogs. The aim of this study was to determine the effect of cefovecin in the empirical treatment of bacterial lower respiratory tract disease in shelter dogs with clinical, biochemical, and oxidative parameters by comparing it with ceftriaxone, a member of the 3rd generation of cephalosporins.

MATERIAL AND METHODS

The study was approved by the Hatay Mustafa Kemal University Animal Experiments Local Ethics Committee (Approval number, 2015/10-10; Approval date, 30 Dec, 2015).

Study design and animals

The study population consisted of fifty mixed-breed shelter dogs (12 to 48 months of age) with respiratory tract infection symptoms transported from Hatay Metropolitan Municipality Temporary Animal Rehabilitation Centre to Hatay Mustafa Kemal University Veterinary Health, Application and Research Hospital. Dogs having respiratory disease signs such as fever, lethargy, anorexia, ocular and nasal discharge, sneezing, expectoration, cough, and abnormal lung sounds were included (n= 32) in the study. Dogs with comorbid respiratory tract disease or a medication history for existing respiratory tract disease were excluded from the study (n= 18). All dogs diagnosed with LRTD (n= 32) based on clinical, radiographic and laboratory examinations were divided into treatment groups as Cefovecin Group-Group 1 (n = 16) and Ceftriaxone Group-Group 2 (n = 16).

Clinical examination

The examinations of all dogs were performed by the same veterinary physician before (day 0), during (first four days and day 8), and after (day 15) the treatment. And, modified scoring parameters [2] were used to evaluate the health status of all dogs (Table 1).

Table 1. Scores and evaluation of clinical parameters.

PARAMETERS	EVALUATION/SCORES				
	0	**1**	**2**	**3**	**4**
Clinical Status		**Normal**	**Mild** (has food and water intake, and environmental relation)	**Moderate** (No appetite, has water intake, poor environmental relation)	**Severe** (No appetite, water intake too low, depressive)
Mucous Membranes		**Normal**	**Mild** (Less hyperemia)	**Moderate** (Diffuse hyperemia)	**Severe** (Diffuse dark hyperemia, plumped conjunctival vessels)
Tracheal Sensitivity	**None**	**Available**			
Nasal Discharge	**None**	**Serous**	**Seromucous**	**Mucous**	**Purulent**
Auscultation		**Normal**	**Mild** (Hardened vesicular and bronchial sounds)	**Moderate** (Wet rales, crackling and rustling sounds)	**Severe** (Dry rales and wheezing / friction sounds)
Cough		**None**	**Mild** (with long intervals)	**Moderate** (with short intervals)	**Severe** (Continuous)

Laboratory analyses

Anticoagulated (BD PRESET™, BD Diagnostics, Franklin Lakes, USA; BD EDTA K2, BD Diagnostics, Franklin Lakes, USA) and non-anticoagulated (Vacutainer®, BD Diagnostics, Franklin Lakes, USA) blood samples were collected from all dogs before (day 0), during (day 8), and after (day 15) treatment via cephalic or jugular venipuncture. All dogs underwent a complete blood count (CBC) (Diatron® Abacus Junior Vet, Budapest, Hungary) and venous blood gas analysis (IRMA® TRUPOINT™, New Jersey, USA). Malondialdehyde (MDA), total oxidant capacity (TOC), total antioxidant capacity (TAC) levels (Beckman Coulter AU480 Chemistry Analyzer, USA) and routine serum biochemistry parameters (Siemens Advia 1800® Clinical Chemistry System, Germany) were measured in blood serum samples.

Radiological examination

Radiographic imaging was performed before BAL collection. Two-way (Laterolateral-L/L and Ventrodorsal-V/D) chest radiographs (60-80 kV and 5-20 mAs, Regius ∑II, Konica Minolta, Tokyo, Japan) for pre-treatment (day 0) and post-treatment (day 15) were carried out. Chest radiographs were evaluated by the same expert veterinary surgeon in terms of increase in radiopacity (alveolar, interstitial, bronchial, and vascular structure) and decrease (hyperlucency), presence of mass, and calcification. According to the prevalence and density of the lesions in the lung lobes, they were scored as none (0), mild (1), moderate (2), and severe (3).

Collection and examination of bronchoalveolar lavage fluid

For microbiological analysis, BAL was collected by a non-bronchoscopic method from all dogs included in the study twice, before and after treatment. Animals were short-time anesthetized with Ketamine HCl (10-20 mg/kg, b.w., i.m., Ketasol® 10%, Richter Pharma AG, Wels-Austria) and Xylazin (1-2 mg/kg, b.w., i.m., Rompun® 2%, Bayer, Germany) to obtain BAL. A 20mL sterile saline solution was used for the collection of

BAL samples. BAL samples were collected by using a sterile propylene catheter measuring 2.67 mm × (8 ch) × 500 mm (Feeding tube, Bıçakçılar®, Turkey) via the inserted sterile endotracheal tube, and were sent to the microbiology laboratory for bacteriological analysis within an hour. BAL collection was performed as described previously [2].

Microbiological analysis

BAL samples were quantitatively inoculated on Bordet Gengou agar (Conda pronadisa, Spain), 5% sheep blood agar (bioMerieux, France), EMB (eosin methylene blue) agar (LABM, United Kingdom), and chocolate agar (Conda pronadisa, Spain), and incubated at 37°C for 48 h. The incubation period was extended in the presence of poor culture. BAL samples were also stained with the Gram staining method and examined under the microscope at ×100 and ×1000 magnifications. The presence of less than 10 epithelial cells and more than 25 leukocytes at x100 magnification and the presence of leukocytes, epithelial cells, bacteria, and intracellular bacterial cells at x1000 magnification were considered as infection. Isolated bacteria were identified with the Vitek 2 Automatized System (BioMerieux, France). Post-treatment BAL samples were cultured and evaluated in the same way.

The treatment protocol

The treatment protocol was administered as described in Table 2. Antibacterial drug dosage, administration route, and duration were created using literature knowledge [31,32] and recommendation of manufacturers. Treatment responses in dogs in both groups were evaluated by clinical scores (Table 1) on days 1–5, 8, and 15. Dogs were kept in their individualized compartments and fed with commercial dog food during the treatment period, and clean water was provided daily.

Table 2. Treatment protocol of groups and its applications.

Medicines	Group 1 / Cefovecin Group	Group 2 / Ceftriaxone Group
Antibacterial drug	Cefovesin sodium (8 mg/kg bw, S.C., single dose, Convenia®, Zoetis)	Ceftriaxone sodium (15 mg/kg bw, IM, SID, for 14 days, Novosef®, Zentiva)
Nonsteroidal anti-inflammatory drug	Flunixin meglumine (1.1 mg/kg bw, IM, SID, for 5 days, Flumed®, Alke)	Flunixin meglumine (1.1 mg/kg bw, IM, SID, for 5 days, Flumed®, Alke)
Expectorant	Bromhexine HCl (1.7 ml/per 10kg bw., I.M., for 14 days, Mucolit®, Provet)	Bromhexine HCl (1.7 ml/per 10kg bw., I.M., for 14 days, Mucolit®, Provet)

Statistical methods

Considering the number of individuals in the groups ($n<30$), non-parametric tests were applied. The Mann-Witney test was used to compare obtained data between Groups 1 and 2. The Friedman and Wilcoxon tests were used for in-group comparisons. Statistical analyses were performed using SPSS v22 (Armonk, NY: IBM Corp.) and P value < 0.05 was considered significant for all tests.

RESULTS

Differences in clinical scores between groups can be found in Table 3. When evaluated in terms of clinical status, compared to day 0, recovery was observed on the second day ($P<0.05$) and on the third day ($P<0.05$) for Groups 1 and 2, respectively. The alleviation (return to pink) in mucous membranes in groups one and two was determined on day 1 ($P < 0.05$) and day 2 ($P < 0.001$), respectively. A decrease in tracheal sensitivity was seen on day 8 ($P < 0.05$) in Group 1 and on day 15 ($P < 0.05$) in Group 2. For both groups, a decrease and characteristic changes in nasal discharge were observed on day 2 ($P < 0.05$). In Groups 1 and 2, an improvement in auscultation was determined on day 2 ($P < 0.05$) and on day 3 ($P < 0.05$), respectively. Recovery from cough in Groups 1 and 2 was detected on day 1 ($P < 0.05$) and on day 2 ($P < 0.05$), respectively. There were no differences in terms of body temperature, pulse, and respiration rate per minute between days within groups. Although differences were detected in the body temperature ($P < 0.05$), pulse ($P < 0.05$) and respiration rate per minute ($P < 0.05$) between the groups, they ranged within the reference values (Table 3). Except for nasal discharge ($P < 0.05$), any differences in other clinical parameters were not detected between the groups (Table 3).

Table 3. Clinical score differences between and within groups (Group-1, n: 16; Group-2, n: 16) according to days.

Clinical Scores	Groups	Median (min-max) Day 0	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15	P*
CS	G1	3^{a} (2-4)	3^{a} (2-4)	3^{b} (2-4)	3^{b} (2-4)	3^{b} (2-4)	2^{c} (1-3)	1^{d} (1-4)	0.000
	G2	3^{a} (2-4)	3^{a} (2-4)	3^{a} (1-4)	2^{b} (1-4)	2^{b} (1-4)	2^{c} (1-3)	1^{d} (1-3)	0.000
	P**	0.382	0.764	0.839	0.182	0.139	0.252	0.493	
MM	G1	3^{a} (3-4)	3^{b} (2-4)	2^{c} (1-4)	1^{cd} (1-4)	1.5^{cd} (1-3)	1^{d} (1-3)	1^{d} (1-4)	0.000
	G2	2.5^{a} (2-4)	2^{a} (1-4)	1.5^{b} (1-3)	1.5^{bc} (1-4)	1^{bc} (1-3)	1^{bc} (1-3)	1^{c} (1-3)	0.000
	P	0.139	0.445	0.377	0.967	0.443	1.000	0.924	
TS	G1	1^{a} (0-1)	1^{ab} (0-1)	1^{ab} (0-1)	1^{ab} (0-1)	1^{ab} (0-1)	1^{b} (0-1)	0^{c} (0-1)	0.000
	G2	1^{a} (0-1)	1^{a} (0-1)	1^{a} (0-1)	1^{ab} (0-1)	1^{ab} (0-1)	0.5^{ab} (0-1)	0^{b} (0-1)	0.008
	P	0.632	1.000	1.000	0.699	0.453	0.483	0.422	
ND	G1	4^{a} (4-4)	4^{a} (4-4)	4^{b} (2-4)	3.5^{bc} (2-4)	2^{c} (1-4)	2^{c} (0-4)	0^{d} (0-4)	0.000
	G2	4^{a} (2-4)	3.5^{ab} (1-4)	2.5^{b} (1-4)	2^{bc} (1-4)	2^{c} (1-4)	1^{d} (0-4)	0.5^{d} (0-4)	0.000
	P	0.017	0.001	0.149	0.208	0.505	0.028	0.722	
AU	G1	3^{a} (2-4)	3^{ab} (2-4)	2^{b} (2-4)	2^{cd} (1-3)	2^{bc} (1-4)	2^{cd} (1-3)	1^{e} (1-2)	0.000
	G2	3^{a} (2-4)	$2,5^{ab}$ (2-4)	3^{abc} (1-4)	2^{bcd} (1-4)	2^{cd} (1-3)	2^{d} (1-3)	1^{e} (1-3)	0.000
	P	0.825	0.476	0.296	0.921	0.516	0.952	0.344	
COU	G1	3^{a} (2-3)	2^{b} (1-3)	2^{cde} (1-3)	2^{bc} (1-3)	2^{bcd} (1-3)	2^{de} (1-3)	1^{e} (1-3)	0.000
	G2	3^{a} (2-4)	2.5^{abd} (1-4)	2^{bcd} (1-4)	2^{cd} (1-3)	2^{cd} (1-4)	2^{de} (1-3)	1^{e} (1-3)	0.000
	P	0.911	0.657	0.585	0.489	0.796	0.883	0.829	
T	G1	39.60 (38.30-40.90)	39.20 (38-41.30)	39.45 (38.10-41)	39.30 (37.60-41.60)	39.05 (38.20-40.90)	39.15 (38.10-40.80)	38.95 (36.90-39.90)	0.267
	G2	39.20 (37.70-42.50)	39.17 (38.30-39.70)	38.80 (38.08-39.68)	38.78 (38.23-40.56)	38.82 (37.70-40.55)	38.81 (37.96-40.05)	39.15 (38.40-39.80)	0.154
	P	0.428	0.584	0.042	0.584	0.439	0.406	0.395	
P	G1	100 (52-144)	116 (64-172)	110 (68-176)	112 (68-160)	118 (100-160)	114 (88-176)	112 (72-160)	0.220
	G2	94 (60-140)	90 (68-156)	92 (64-140)	94 (68-128)	98 (64-148)	114 (72-156)	93.50 (68-160)	0.254
	P	0.610	0.086	0.045	0.012	0.007	0.985	0.130	
R	G1	28 (16-144)	34 (16-128)	40 (16-104)	36 (16-120)	34 (20-68)	28 (16-84)	24 (12-48)	0.057
	G2	24 (12-64)	28 (16-48)	24 (16-48)	28 (20-56)	28 (16-48)	28 (20-60)	24 (16-46)	0.358
	P	0.436	0.325	0.009	0.080	0.042	0.400	0.894	

G1: cefovecin treated group; G2: ceftriaxone treated group

*: defines the group's inter-day importance.

**: defines the significance between the groups based on days

- Superscripts in the same row define the difference between days within the groups.
- CS: Clinical Status, MM: Mucous Membranes, TS: Tracheal Sensitivity, ND: Nasal Discharge, AU: Auscultation, COU: Cough, T: Body Temperature, P: Pulsation/min, R: Respiration/min
- Clinical status, mucous membrane, auscultation and cough were scored with in 1 to 4. Nasal discharge was scored with in 0 to 4 and tracheal sensitivity was scored as none (0) or available (1).

There was no significant difference in the CBC data between the groups except the value of platelets on the 8th day (P = 0.007) and haemoglobin levels on the 15th day (P = 0.025) (Table 4). In the evaluation of venous blood gas findings (Table 4), it was found that while the difference in Group 1 daily data was not detected, there was an increase (P = 0.006) in pCO2 level between 0-8 days and a decrease (P = 0.002) between 8-15 days in Group 2. In terms of pH, HCO3, and tCO2 values in venous blood gas, it was determined that there was no within-group difference in both groups.

Table 4. Evaluation of groups (G1, n: 16; G2, n: 16) in terms of complete blood count and venous blood gas results.

Parameters	Groups	Day 0 Median (Min-Max)	Day 8 Median (Min-Max)	Day 15 Median (Min-Max)	P*
White Blood Cells × 10^9/L	G1	22.05 (8.64-64.88)	18.52 (4.37-37.78)	21.80 (3.10-40.95)	0.345
	G2	19.98 (7.61-48.35)	15.83 (8.48-28.97)	14.37 (4.93-26.45)	0.174
	P**	0.291	0.598	0.498	
Lymphocyte × 10^9/L	G1	1.09 (0.13-2.90)	1.61 (0.15-6.51)	1.51 (0.23-8.90)	0.144
	G2	1.35^{c} (0.08-3.39)	1.67^{ab} (0.21-5.12)	1.59^{abc} (0.19-4.11)	0.028
	P	0.763	0.678	0.585	
Granulocyte × 10^9/L	G1	19.61 (6.96-58.10)	14.80 (2.17-37.24)	20.16 (3.95-89.10)	0.570
	G2	16.94 (4.92-42.53)	12.61 (5.89-27.87)	12.11 (3.81-24.39)	0.185
	P	0.346	0.474	0.243	
Red Blood Cells × 10^{12}/L	G1	5.89^{ab} (4.79-8.51)	6.11^{a} (3.29-9.06)	5.41^{c} (2.59-6.76)	0.001
	G2	6.32 (4.43-7.67)	6.27 (3.82-7.57)	5.57 (4.57-7.41)	0.099
	P	0.534	0.572	0.327	
Haemoglobin g/dL	G1	10.90^{ab} (8.50-16.00)	11.20^{a} (5.50-19.10)	9.55^{c} (5.60-12.90)	0.002
	G2	12.15 (8.30-15.50)	12.45 (6.80-14.20)	10.60 (8.60-13.40)	0.177
	P	0.235	0.109	0.025	
Haematocrit %	G1	36.16^{ab} (28.36-52.10)	37.31^{a} (20.41-59.01)	32.57^{c} (20.20-44.00)	0.028
	G2	39.75 (27.82-47.98)	39.90 (22.79-44.20)	35.34 (29.19-42.61)	0.099
	P	0.228	0.376	0.097	
Platelets × 10^9/L	G1	166.50 (0-468)	185 (12-581)	171 (0-487)	0.646
	G2	296.50 (89-472)	361 (45-812)	292.50 (32-509)	0.185
	P	0.097	0.007	0.073	
pH	G1	7.36 (7.25-7.41)	7.32 (7.19-7.44)	7.35 (7.31-7.40)	0.236
	G2	7.355 (7.27-7.42)	7.32 (7.23-7.39)	7.35 (7.29-7.38)	0.083
	P	0.438	0.394	0.352	
pCO_2	G1	40.15 (29.80-56.90)	43.05 (32.10-57.50)	42.20 (32.80-55.20)	0.368
	G2	43.20^{b} (30.40-63.40)	48.75^{a} (39.80-59.20)	42.95^{bc} (36.50-49.30)	0.003
	P	0.522	0.132	0.777	
HCO_3	G1	20.95 (14.80-35.20)	23.15 (17.40-28.50)	23.85 (18.40-28.10)	0.236
	G2	23.70 (17.60-29.90)	24.85 (17.90-32.20)	23.30 (19.70-27.10)	0.152
	P	0.152	0.193	0.706	
tCO_2	G1 (n:16)	22.30 (15.70-36.90)	24.45 (18.40-30.30)	25.20 (19.50-29.70)	0.210
	G2 (n:16)	25.10 (18.50-31.90)	26.45 (19.30-34.10)	24.60 (20.90-28.60)	0.87
	P	0.169	0.200	0.720	

*: defines the group's inter-day importance.
**: defines the significance between the groups based on days.
Superscripts in the same row define the difference between days within the groups.

Blood serum Alanine Aminotransferase (ALT) enzyme activity was higher in Group 1 compared to Group 2 before treatment (day 0) (P = 0.010). Total protein levels on the 8th day (P = 0.026) and the 15th day (P = 0.044) were found to be lower in Group 1 compared to Group 2, and creatinine levels on the 8th day (P = 0.018) and the 15th day (P = 0.001) were found to be lower in Group 1 compared to Group 2 (Table 5). In serum oxidative stress parameters, it was determined that the TAC levels in Group 1 were lower (P = 0.014) and the antioxidant index was higher (P = 0.022) compared to Group 2 before the treatment (day 0) (Table 5).

Table 5: The blood chemistry results by days of groups (Group-1, n: 16; Group-2, n: 16).

Parameters	Groups	Day0 Median (Min-Max)	Day8 Median (Min-Max)	Day15 Median (Min-Max)	P*
Aspartate Aminotransferase IU/L	G1	27.50^{c} (17-55)	34^{ab} (22-157)	35^{a} (21-334)	0.001
	G2	21^{c} (15-46)	37^{ab} (14-48)	32^{b} (22-81)	0.001
	P**	0.131	0.925	0.386	
Alanine Aminotransferase IU/L	G1	17^{c} (6-179)	25^{ab} (12-151)	23^{b} (11-64)	0.004
	G2	11.50^{c} (5-22)	21.50^{ab} (10-36)	23.50^{a} (11-51)	0.000
	P	0.010	0.151	0.584	
Alkaline phosphatase IU/L	G1	72 (28-397)	83 (25-256)	66.50 (24-262)	0.058
	G2	50 (26-121)	53 (27-163)	57.50 (22-178)	0.895
	P	0.235	0.109	0.181	
γ - Glutamyl transferase IU/L	G1	7.0^{c} (5-13)	9.50^{a} (5-23)	7.50^{bc} (6-13)	0.006
	G2	8.0 (7-10)	8.0 (7-10)	8.0 (6-10)	0.347
	P	0.122	0.101	0.922	
Total Protein g/dL	G1	5.85 (5.19-7.43)	5.63 (4.15-6.70)	5.85 (3.34-7.72)	0.269
	G2	5.94 (4.62-8.38)	6.17 (5.06-8.16)	6.24 (5.31-8.01)	0.185
	P	0.925	0.026	0.044	
Blood Urea Nitrogen mg/dL	G1	9.15^{c} (6-17)	12.60^{ab} (6.70-96)	14.40^{a} (7.40-19.90)	0.008
	G2	12.60 (4.40-28.40)	15.20 (7-32)	12.65 (4.80-38.50)	0.099
	P	0.142	0.274	0.283	
Creatinine mEq/L	G1	0.56 (0.42-0.89)	0.58 (0.35-0.96)	0.54 (0.22-0.79)	0.125
	G2	0.50^{c} (0.40-0.77)	0.73^{ab} (0.45-0.99)	0.70^{b} (0.52-0.93)	0.002
	P	0.624	0.018	0.001	
Total Bilirubin mg/dL	G1	0.03 (0-0.20)	0.02 (0-0.19)	0.03 (0-8.89)	0.404
	G2	0.01^{bc} (0-0.04)	0.01^{c} (0-0.03)	0.03^{a} (0-0.10)	0.018
	P	0.153	0.522	0.675	
Direct Bilirubin mg/dL	G1	0.0 (0-0.08)	0.0 (0-0.05)	0.0 (0-6.62)	0.913
	G2	0.02 (0-0.03)	0.02 (0-0.04)	0.02 (0-0.04)	0.113
	P	0.051	0.194	0.078	
TAC mmol Trolox Eq/L	G1	0.80 (0.60-1.00)	0.85 (0.70-1.00)	0.90 (0.20-1.90)	0.127
	G2	0.90^{a} (0.70-1.30)	0.90^{bc} (0.80-1.20)	0.80^{c} (0.10-1.00)	0.001
	P	0.014	0.361	0.222	
TOC lmol H_2O_2 Eq/L	G1	90.65 (62.30-111.40)	92.35 (83.10-102.20)	90.30 (0.80-98.40)	0.185
	G2	91.45 (0.80-104.90)	92.75 (0.60-104.50)	89.45 (0.80-101.40)	0.646
	P	0.895	0.497	0.895	
MDA nmol/mL	G1	2.055 (1.42-5.39)	2.270 (1.00-5.50)	2.475 (1.40-4.90)	0.779
	G2	2.290 (0-5.34)	2.080 (1.58-8.30)	2.025 (0-4.37)	0.740
	P	0.336	0.692	0.059	
Antioxidant index (TOC/TAC × 100)	G1	11574.31^{ab} (7787.50- 15471.43)	11369.44^{b} (9444.44- 13542.86)	10138.89^{c} (400.00- 12250.00)	0.015
	G2	9468.64^{bc} (88.89- 14828.57)	10456.25^{ab} (66.67- 13062.50)	10694.44^{a} (800.00- 12785.71)	0.047
	P	0.022	0.243	0.474	

G1: cefovecin treated group; G2: ceftriaxone treated group
*: defines the group's inter-day importance.
**: defines the significance between the groups based on days.
•Superscripts in the same row define the difference between days within the groups.

Radiographic data and scores of groups can be found in Table 6. Increased opacity was detected in all cases. If the lesions encountered in all cases are ranked from mild to severe, it can be said that vascular,

alveolar, interstitial, and bronchial patterns are observed. Considering the parameters determined for the lesions, in the radiographs of Group 1, vascular (n = 2), alveolar (n = 5), interstitial (n = 7) and bronchial (n = 7); vascular (n = 1), alveolar (n = 5), interstitial (n = 4) and bronchial (n = 3) healing were observed in Group 2. The lesions were found to have decreased in both groups following treatment. When the total radiography scores (before and after treatment) were evaluated, decreases, increases, and no change in scores were detected in 10 (62.50%), 4 (25%), and 2 (12.50%) of Group 1 animals, and were detected in 7 (43.75%), 4 (25%), and 5 (31.25%) of Group 2 animals, respectively (Table 6). When comparing the two groups, the level of radiographic improvement was not statistically significant (P>0.05).

Table 6. Radiography score results of the Groups.

Case No	RST	Alveolar		Interstitial		Bronchial		Vascular		∑ Score	
		Gp 1	Gp 2	Gp 1	Gp 2	Gp 1	Gp 2	Gp 1	Gp 2	Gp 1	Gp 2
1	BT	2	1	2	2	3	2	2	1	9	6
	AT	2	1	3	3	2	3	1	1	8	8
2	BT	2	2	2	3	3	3	1	1	8	9
	AT	2	2	2	3	2	2	1	1	7	8
3	BT	2	1	3	3	3	3	1	1	9	8
	AT	2	2	2	3	3	2	1	1	8	8
4	BT	1	2	2	3	2	3	1	1	6	9
	AT	1	1	2	2	2	3	1	1	6	7
5	BT	2	1	2	2	3	2	1	1	8	6
	AT	2	2	1	2	3	2	1	1	7	7
6	BT	2	1	2	2	3	2	1	1	8	6
	AT	1	2	2	3	2	2	1	1	6	8
7	BT	2	1	2	2	3	2	1	1	8	6
	AT	1	1	1	2	2	2	1	1	5	6
8	BT	2	2	3	3	3	3	2	2	10	10
	AT	1	1	2	2	3	2	2	1	8	6
9	BT	1	1	2	2	2	3	1	1	6	7
	AT	2	2	2	2	3	3	1	1	8	8
10	BT	1	1	2	2	2	3	1	1	6	7
	AT	1	1	2	2	3	3	1	1	7	7
11	BT	2	2	2	3	3	3	1	1	8	9
	AT	3	1	3	2	3	3	1	1	10	7
12	BT	2	1	3	2	3	2	1	1	9	6
	AT	3	1	2	2	2	2	1	1	8	6
13	BT	3	2	2	2	2	2	1	1	8	7
	AT	1	1	3	2	3	2	1	1	8	6
14	BT	2	2	3	3	3	3	1	2	9	10
	AT	1	2	2	2	1	3	1	2	5	9
15	BT	2	2	3	2	2	2	2	1	9	7
	AT	2	1	2	2	2	2	1	1	7	6
16	BT	2	2	2	3	3	3	0	1	7	9
	AT	2	2	3	3	2	3	1	1	8	9
P		0.366	0.739	0.366	0.414	0.166	0.317	0.564	0.317	0.117	0.413

RST: Radiography Shooting Time, BT: Before Treatment, AT: After Treatment. Gp1: cefovecin treated group, Gp2: ceftriaxone treated group

In the pre-treatment, BAL cultures of dogs in Group 1 (n=16), *B. bronchiseptica* (11/16, 68.75%), *Streptococcus* spp. (5/16, 31.25%), *Staphylococcus* spp. (3/16, 18.75%), and *K. pneumoniae* (1/16, 6.25%); in the post-treatment, *Staphylococcus* spp. (6/16, 37.5%), *Streptococcus* spp. (2/16, 12.5%) and *B. bronchiseptica* (2/16, 12.5%) were isolated and identified (Table 7). In the pre-treatment BAL cultures of dogs in Group 2 (n:16), *Pasteurella canis* (4/16, 25%), *B. bronchiseptica* (4/16, 25%), *Streptococcus* spp. (3/16, 18.75%), *Escherichia coli* (2/16, 12.5%), *S. aureus* (1/16, 6.25%), *Pasteurella aerogenes* (1/16, 6.25%), and *Klebsiella oxytoca* (1/16, 6.25%); in the post-treatment, *E. coli* (3/16, 18.75%) and *B. bronchiseptica* (1/16, 6.25%) were isolated and identified (Table 7). Although only five cases in Group 1 had initial bacterial agents isolated after treatment, the agents isolated after treatment were shown to be distinct from the cultures obtained before treatment in Group 2. When considered on a case-by-case basis with bacterial isolation before and after treatment, the anti-bacterial effects of cefovecin sodium used in Group 1 and ceftriaxone sodium used in Group 2 were determined as 68.75% (n: 11/16) and 100% (n: 16/16), respectively.

Table 7. Bronchoalveolar lavage fluid culture results of Groups.

	Group 1		Group 2	
CS	**BT**	**AT**	**BT**	**AT**
1	*Bordetella bronchiseptica*	*Staphylococcus* spp.	*Pasteurella canis*	*Escherichia coli*
2	*Staphylococcus* spp. *Bordetella bronchiseptica*	*Staphylococcus* spp.	*Bordetella bronchiseptica*	*Escherichia coli*
3	*Staphylococcus* spp. *Bordetella bronchiseptica*	*	*Escherichia coli*	*Bordetella bronchiseptica*
4	*Bordetella bronchiseptica*	*Staphylococcus* spp.	*Streptococcus* spp.	*Escherichia coli*
5	*Streptococcus* spp.	*Streptococcus* spp.	*Escherichia coli*	*
6	*Bordetella bronchiseptica*	*	*Klebsiella oxytoca*	*
7	*Streptococcus* spp.	*	*Pasteurella canis*	*
8	*Klebsiella pneumonia*	*Streptococcus* spp.	*Bordetella bronchiseptica*	*
9	*Bordetella bronchiseptica*	*Bordetella bronchiseptica*	*Bordetella bronchiseptica*	*
10	*Streptococcus* spp. *Bordetella bronchiseptica*	*Staphylococcus* spp.	*Pasteurella canis*	*
11	*Streptococcus* spp. *Bordetella bronchiseptica*	*Staphylococcus* spp.	*Pasteurella canis*	*
12	*Bordetella bronchiseptica*	*Bordetella bronchiseptica*	*S. aureus*	*
13	*Streptococcus* spp.	*	*Bordetella bronchiseptica*	*
14	*Bordetella bronchiseptica*	*	*Streptococcus* spp.	*
15	*Bordetella bronchiseptica*	*	*Streptococcus* spp.	*
16	*Staphylococcus* spp.	*Staphylococcus* spp.	*Pasteurella aerogenes*	*

CS: Case number, BT: Before treatment, AT: After treatment
*: Bacterial growth was not identified.

DISCUSSION

After integumentary and digestive system problems in shelter dogs, the most commonly encountered problem is respiratory system disease [33]. Among the diseases of the respiratory system, canine infectious respiratory disease (CIRD) is the most common [34]. Clinical monitoring is very important to evaluate the prognosis of respiratory tract diseases. This is because CIRD is characterised by a dry cough and nasal discharge, showing an acute onset of spread among dogs [35]. It is seen that clinical monitoring has been carried out in several studies conducted on dogs with respiratory tract diseases [2,12,36]. In a study, authors [36] scored based on the character of the nasal discharge, the severity of the cough and body temperature in order to monitor the clinical situation, and benefited from this scoring in the clinical evaluation of the animals during the study. And they emphasize that as the severity of the disease increases, the clinical score also increases. In a study on the aetiology of respiratory disease in dogs, the authors [34] performed clinical scoring with cough, nasal discharge, anorexia, and depression. In another study related to upper respiratory tract disease in cats, clinical scoring was used to evaluate the response to treatment with cefovecin for a period of fourteen days, and parameters such as cough, oculonasal discharge, sneezing, and mobility were used for this purpose [37]. Authors [37] state that there was a significant difference in behaviour on the fifth day in the group treated with cefovecin compared to the first day in the scoring, but there was no difference in terms of oculonasal discharge during the treatment. Unlike Litster and coauthors [37], in the presented study, a significant difference in the clinical status compared to pre-treatment in the cefovecin group was determined after the first week, and the difference in terms of nasal discharge compared to the first day was determined at the end of the treatment. When the clinical parameters were generally evaluated, there was a rapid improvement after the first week in both groups. Therefore, it was concluded that monitoring the clinical parameters discussed in the study for at least one week during the treatment of respiratory tract disease would be beneficial in order to evaluate the effectiveness of the treatment.

The complete blood count, widely used in clinics [38], is an auxiliary method that provides an assessment of the presence of infection in sick animals [39,40]. Although an increase in the leukogram can be seen in LRTD [39,40], CBC abnormalities are seen inconsistently with bacterial pneumonia in both dogs and cats [14,38]. In the study, similar to the results of a study [12], at the beginning of treatment, the high white blood cell value in both groups can be considered as a sign of active inflammation. It is stated that serum

biochemistry changes in respiratory tract diseases are not specific [14,38,39,41]. Similar to Darcy and coauthors [41], in the study, it was determined that there was no change in the blood biochemistry profile and it ranged within the reference limits, and it was considered that the treatments applied in both groups did not have side effects, likely hepatotoxicity, nephrotoxicity, etc.

Although the primary goal of the respiratory system is gas exchange [12,15], the lungs also play a role in maintaining acid-base balance [12]. However, when there is a pathological process that can affect the lungs, as in respiratory diseases, these functions are affected and the organism's compensation mechanisms come into play [12,15]. When the venous blood gas parameters were evaluated in the study, it was found that there was no statistical difference between the groups. However, when the values are examined, the increase in HCO3, which is the compensation mechanism's response to the pH decrease caused by the increase in pCO2 formed in the first week of treatment, stands out and demonstrates that the compensation mechanism works [12]. After the first week, the reverse changes in these values may indicate that the inflammation in the lungs has subsided and begun to return to normal, and thus ventilation and metabolic improvements are provided.

Similar to previous studies [42,43], it was found that there was no statistically significant difference between the groups in terms of MDA, the final product of oxidation reactions [44]. On the other hand, it was also found that the MDA value of the study was above the data average of a study [45] that was previously conducted to determine the reference range in healthy dogs. Although there is no statistical difference, in the light of the study results in terms of oxidative stress, both higher levels of TAC and a lower oxidative stress index in the cefovecin treated group suggest that it may have an antioxidant potential in respiratory tract infections.

Radiographic examination is essential for the clinical evaluation of pneumonia cases [14,15]. As a result of inflammatory cell infiltration caused by bacterial, viral, and allergic inflammation of the lungs, the density of bronchial walls and peri-bronchial connective tissues rises, and bronchial structures with air bronchograms appear on radiography [46]. Classical radiographic findings of bacterial bronchopneumonia cases include cranioventral alveolar involvement [14,15]. The reason for this situation is that local defence mechanisms are not effective in the cranioventral lung lobes [14]. Lesions in the caudal lobes suggest more haematogenous spread or inhaled infection [14]. In a study in which the effects of short-term (< 4 weeks) and long-term (> 4 weeks) treatment of bacterial pneumonia cases were evaluated by radiography, it has been reported that in the radiographic evaluations of dogs, there is no difference between short-term and long-term treatments on radiographic images of lung tissue [47]. However, in the radiographs of almost all cases in the presented study, it was determined that the most dominant structure was the bronchial pattern. These structures were found to be able to spread to all lobes, especially the caudal lung lobes, in a linear and reticular fashion due to the increase in opacity, and images similar to dried tree branches were detected. Tubular air bronchograms were also found between the linear and reticular structures. After the treatments, it was determined that these air bronchograms widened, the bronchial walls became thinner, and the amount of normal lung tissue appearance increased. Bronchopneumonia is generally a condition characterized by the formation of mixed bronchial and interstitial structures. This situation may be accompanied by multifocal alveolar structure from time to time [14]. Whichever structural element is dominant in the radiography, the disease is generally evaluated in that category. In the evaluation of radiographs in this study, it can be said that the bronchial structure is the most dominant, and the interstitial structure is observed secondly. When the radiographic, clinical, and microbiological analysis findings of the presented study and the literature knowledge [27] are combined, it may be said that shelter dogs treated in this study suffer from bacterial bronchopneumonia.

Many microorganisms of viral and bacterial origin may play a role alone or together in the aetiology of respiratory disease in dogs [38]. The lower respiratory tract has a unique defence network. The nasopharynx, mucociliary clearance, and cough clear larger than 10µm particles. However, particles smaller than 3µm accumulate in the alveoli. Bacteria often overcome the upper respiratory tract defences when inhaled in droplets or aspirated. So, in healthy animals, bacteria are always isolated from the lower respiratory tract. But unless the total bacterial density, high virulence, and associated direct damage strain the pulmonary defence system, a healthy animal can mostly clear the bacteria from the lower respiratory tract [14]. In previous studies, it is known that various bacterial agents such as *B. bronchiseptica*, *Staphylococcus intermedius*, *Pseudomonas* spp., *Pasteurella* spp., *Escherichia coli*, *Klebsiella* spp., and *Acinetobacter* spp. were isolated in shelter dogs suffering from respiratory disease [2,7,11,18,48]. Epstein and coauthors [33] reported that they isolated mostly gram-negative non-enteric bacteria in respiratory patients and gram-negative enteric bacteria in dogs with respiratory failure. It is reported that *K. oxytoca*, an opportunistic bacterium, can cause serious infectious diseases [49]. In a study, it was reported that *B. bronchiseptica* (10.26%) was isolated from dogs with respiratory tract infection [34]. In the same study, it is emphasised that

B. bronchiseptica is less isolated from animals with very severe clinical scores, while bacterial agents such as *Mycoplasma cynos* and *Mycoplasma canis* are more isolated in severe cases. In their study, Darcy and coauthors [41] expressed that *Pasteurella* spp., *E. coli*, *Staphylococcus* spp., and *B. bronchiseptica* are commonly isolated agents, respectively. In the presented study, isolated and identified agents (Table 7) were determined similar to previous studies [2,12,33,34]. Considering the data of this study and previous studies, it is seen that more than one and different bacterial species are isolated and identified in canine bacterial lower respiratory disease. It is thought that this difference may arise from individual and environmental diversity.

In canine infectious respiratory disease, it is stated that even if the primary agents are viral agents, bacterial agents other than viral agents may be included in the disease process and even, in some cases, together [1,38]. In this regard, antibacterial drugs are recommended as first-line treatment in pneumonia cases in veterinary medicine [39]. It would be appropriate to select antibacterial agents according to sensitivity test results in the treatment of infectious respiratory diseases in dogs [27]. However, in animal shelters where animal and work density exist [50], and in cases where these tests cannot be performed, it is reported that an empirical choice can be made considering the possible etiological agents, and aminopenicillin, tetracycline, and cephalosporin group antibiotics can be evaluated among the options [1,18,39,48]. The authors [20] state that antibiotics are prescribed for respiratory system diseases in dogs in Europe and that first and second-generation cephalosporins are also included. According to susceptibility tests in cats and dogs, cefovecin is an antibacterial agent that may be used for respiratory tract infections and may be effective for secondary bacterial infections [27]. Even though cefovecin may be useful in secondary respiratory bacterial infections, it is not effective against *B. bronchiseptica* and *Mycoplasma* spp. [19,27]. The authors [41] found that all *B. bronchiseptica* isolates were resistant to cefovecin, but *Pasteurella* spp. (100%), *Staphylococcus* spp. (100%), and *E. coli* (75%) were sensitive. In another study [51], except for Streptococcus sp. (33.3%), sensitivity for cefovecin was detected for *Enterobacteriaceae*, *Pasteurellaceae*, *Staphylococcus* spp., and *Enterococcus* spp. isolates as 64.3%, 80%, 90.9%, and 50%, respectively. Similar to a study [30], based on a different system infection also in the presented study, the treatment of infection was tried with antimicrobial drugs containing cefovecin sodium and ceftriaxone sodium in dogs with bacterial lower respiratory tract disease formed naturally. According to the clinical, laboratory, and bacteriological results of the study, the efficacy of treatment protocols created with cefovecin sodium and ceftriaxone sodium was determined as 68.75% and 100%, respectively. Thus, in the light of previous studies and the data of the study presented, it is predicted that although cefovecin sodium seems to be theoretically usable considering one dosage application in the bacterial lower respiratory disease, its clinical success is lower than that of ceftriaxone sodium, which requires repeated administration for 14 days.

The major limitation of the study is that it was designed for an empirical treatment approach for shelter dogs suffering from bacterial lower respiratory disease, so susceptibility tests were not performed. Another limitation of the study is the inability to evaluate the presence of viral agents in the aetiology of all dogs included in the study.

CONCLUSION

Ultimately, during the treatment of respiratory disease, it would be appropriate to perform a clinical scoring and radiographic examination in order to evaluate both the prognosis of the disease and the effectiveness of the selected treatment protocol. In addition, it is considered that, considering the ease of application, animal welfare, and economic feasibility, even though cefovecin sodium seems to be preferable as an antimicrobial drug in the treatment of bacterial lower respiratory diseases, it should not be used as a first choice in the empirical treatment of these diseases, particularly in places such as animal shelters and breeding facilities where respiratory system infections are common. So, cefovecin should be used on a case-by-case basis, as its empirical usage may contribute to the development of bacterial resistance. On the other hand, due to the lack of sufficient and detailed research on the usage of cefovecin in respiratory diseases in dogs, further studies including viral agents' diagnosis, susceptibility results, supportive treatments, dosage regimen, and treatment period should also be conducted in this area.

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