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Efficacy and Safety of Ceftiofur for Treating Serious Respiratory Diseases in Cattle: Clinical, Histopathological, and Microbiological Assessments

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Abstract

Bovine respiratory disease (BRD) is one of the most serious diseases counted for economic loss and extensive usage of antibiotics in cattle. Ceftiofur, a third-generation cephalosporin antibiotic, has been approved for use in cattle in the United States. This study was done to investigate the clinical effect of ceftiofur on calves as well as its efficacy and safety for treating BRD. Thirty Holstein calves from a dairy farm were divided into three groups. Group I served as a health control group. Group II consisted of healthy animals while Group III comprised calves clinically diagnosed with BRD. Both groups II and III received a single subcutaneous injection of ceftiofur (2mg/kg B.W) in the ear. All groups were clinically evaluated at day 0, 7, and 14 after drug administration for illness score, body weight, body gain, feed intake, body temperature, depression score, discharges, ear and coughing score. Pretreatment clinical illness score showed clear signs of BRD (elevation of body temperature and depression). Nasal and ocular discharges were recorded and ranked. Significant increases in ear and coughing score were observed in diseased calves. Group III showed a significant decrease in body weight, body gain and food intake compared to other groups. Non-significant changes between groups I and II were evaluated. In conclusion, ceftiofur could be the drug of choice for treating BRD due to its high efficacy, low adverse effects, and suitability of dosing and administration.

KEYWORDS
Bovine respiratory disease, Ceftiofur, Calves, Clinical Investigations, Efficacy.

INTRODUCTION

Cattle play a central role in the global meat industry, including Egypt. However, bovine respiratory disease (BRD) has been a significant challenge for the beef and dairy sector since the 1960s. BRD poses a threat to veal calf farming, as well as the overall health of cattle during pre-weaning and after-weaning stages. Calf health is a critical concern in the Egyptian livestock industry, impacting the economic viability of cattle operations due to calf losses, treatment costs, and long-term effects on performance (Donovan *et al*., 1998).

Clinical BRD often requires antimicrobial treatment, resulting in increased labor and decreased welfare. It can lead to reduced profitability due to poor performance and mortality rates, which have been estimated at 2.9-5.1% in Europe. The problem is potentially worse in Egypt due to management issues and delayed disease detection. Performance and profitability in veal and beef production can be measured through weight loss, reduced average daily gain, and carcass traits (Becker *et al*., 2021).

BRD is a complex disease caused by a combination of environmental factors, host characteristics, and various microorganisms. Antimicrobial treatments, specifically beta-lactamase, such as cephalosporins, are commonly used to prevent or treat bacterial BRD, including strains producing beta-lactamase. Ceftiofur, a broad-spectrum third-generation cephalosporin, is effective against Gram-negative and Gram-positive bacteria associated with BRD (Pardon *et al*., 2012).

Ceftiofur is frequently used in adult lactating dairy cows for disease complexes, including BRD. Its broad-spectrum therapeutic range, along with zero-hour milk withdrawal periods and short pre-slaughter withdrawal periods, makes it an appealing treatment option. In the United States, ceftiofur is the only third-generation cephalosporin approved for use in cattle and is labeled for the treatment of bovine pneumonia, interdigital necrobacillosis, acute metritis, and mastitis (Arumugham and Cascella 2020).

This study aimed to evaluate the therapeutic efficacy of ceftiofur against BRD, specifically in calves of North-east Egypt. To achieve etiological of the study; the predominant bacteria causing respiratory infections in calves was isolated, the effectiveness of ceftiofur on clinical signs of BRD in infected calves was assessed, and the histopathological changes in the lungs caused by the etiological microorganisms were evaluated.

MATERIALS AND METHODS

The study utilized various laboratory materials and reagents for conducting experiments and analyses.

Drugs

Ceftiofur crystalline free acid (commercially available as Excede®) was obtained from zoites Egypt as a sterile suspension,

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each ml contains 200mg ceftiofur crystalline free acid. Ceftiofur was subcutaneously injected at posterior aspect in the middle third of ear as single dose of 2mg/kg B.W. (Salmon *et al*., 1996).

Animals and experimental design

Thirty Holstein calves (45-70 days old), with an average body weight of 39-60 Kg were subjected to investigation. The study took place at a private dairy farm at Damietta governorate, Egypt. Calves suffering from BRD were visually examined and scored for the presence of fever, nasal and eye discharge, respiratory distress, cough, depression and inappetence (McGuirk, 2008). The calves involved in the study were divided into 3 groups, each consisting of 10 animals. The first group served as the healthy non-treated control group. The second group included healthy treated calves; they were administered ceftiofur subcutaneously at a dosage of 2mg per kilogram of body weight. The third group consisted of BRD clinically diseased calves that were also treated with ceftiofur in the same dose and route as in second group. All animals, regardless of the group they belonged to, were kept under the same conditions of hygiene, nutrition, and management. Clinical examinations for all the calves were conducted based on the methodology described by Radostits *et al*. (2000).

This study was permitted by the Ethics Committee in Faculty of Veterinary Medicine at Suez Canal University (Code no. 2019535).

Clinical Assessment

Clinical respiratory score (CRS) was assessed by utilizing the Wisconsin chart as stated earlier in many articles (McGuirk and Peek, 2014). Calves were examined clinically for body weight, body weight gain, feed intake, body temperature, depression, discharges (nasal and ocular), ear, cough, and lung scores.

A score of 0 (normal and lowest risk of BRD) to 3 (severely abnormal and the highest risk of BRD) was assigned to each parameter.

Tissue samples

Lung samples from calves (n=3) that had died and exhibited signs of pneumonia were selected for sample collection immediately after death, also the lung samples (n=3/group) from control treated healthy and treated diseased groups were collected at day 14. Standardized procedures and good laboratory practices were followed to prevent contamination and ensure data quality. Two parts of lung samples were collected: one for histopathological examination and the other for bacteriological analysis.

For bacteriological examination, samples were collected from the affected areas of the lungs. The samples were stored in individual sterile freezer bags at -80 Celsius degrees until the bacteriological assay.

Bacteriological examination

Media for isolation and biochemical identification

Brain Heart Infusion Broth (Code CM0225) and MRVP medium (Code: CM0043) were obtained from Oxoid in the UK. Blood Agar Base was purchased from Biolab in Egypt. Nitrate reduction medium, also known as nitrate broth (FAO 1992, Code M63 & M64) and tryptone (tryptophane) broth 1% (FAO 1992, Code M111) were procured from Merck, USA. For conducting the catalase test, hydrogen peroxide solution, 3% (FAO 1992, Code R15) was utilized. Kovacs' reagent (FAO 1992, Code R16), methyl red indicator (FAO 1992, Code R19), nitrite detection reagents (FAO 1992, Code R23), Voges-Proskauer (VP) test reagents (FAO 1992, Code R40) and Gram stain (FAO 1992, Code S6) were also employed for specific biochemical tests.

Bacteriological assessments

Lung swabs were plated on blood agar supplemented with 5% sheep blood. The plates were then incubated at 37°C for 24 hours. As the blood agar supports the growth of various bacteria associated with respiratory disorders (including *Pasteurella multocida* and *Staphylococcus aureus*) as well as bacteria not associated with such disorders (such as *Staphylococcus* and *Streptococcus* spp) (Cruickshank *et al*., 1982), morphological and biochemical identifications were performed on the grown bacteria to determine their characteristics. The biochemical recognition included catalase, oxidase, indole, urease, coagulase, MR and VP, hemolysis, nitrate reduction and growth on MacConkey agar tests.

Histopathological inspection

Lung areas were fixed in 10% buffered formalin for 48 hours for histopathological examination. These fixed lung samples were dehydrated using a series of graded alcohol before being embedded in paraffin wax. Thin sections (4-5 micrometers) were obtained from each sample and stained with hematoxylin and eosin (H&E) for histological examination, following the method described by Banchroft *et al*. (1996).

Statistical Analysis

The data obtained in this study was analyzed statistically with analysis of variance technique using SPSS® software (version 18, IBM). Statistically significant differences among the various treatments means were determined by using Least Significant Difference (LSD) test at 5% level of probability.

RESULTS

Clinical findings

In terms of body weight, the control and treated healthy groups did not show any significant differences. However, the diseased group exhibited a significant decrease in body weight compared to the other two groups. Interestingly, the body weight of the diseased group gradually increased over time. Similar statistical differences were observed among the three groups in terms of body weight gain and feed intake, as indicated in Table 1.

Regarding the body temperature, the results indicated a significant elevation in body temperature for the treated diseased group compared to the treated healthy group up to the 7th day. On day 14, there was a noticeable but non-significant reduction in body temperature, with no significant differences observed between the groups.

Throughout the study period, the control and treated healthy groups did not exhibit any signs of BRD. Conversely, the diseased group initially displayed a higher frequency of animals showing severe symptoms of BRD (score 3) on day 0. After treatment with ceftiofur, the majority of animals in the diseased group showed symptoms corresponding to scores 1 and 0, with no animals exhibiting severe symptoms (score 3) or even moderate symptoms (score 2). By day 14, all animals in the diseased group showed

no signs of BRD symptoms. This pattern was consistent across depression score, nasal discharges, ocular discharges, ear score, and cough score.

Table 1. Therapeutic effect of ceftiofur on the body weight, body weight gain and feed intake

Parameters	Groups	Time point		
		Day 0	Day 7	Day 14
Body weight (kg)	Control	50.00±1.37	53.80±1.47	57.20±1.28
	Treated healthy	52.10±1.61	55.40±1.79	58.30±1.88
	Treated diseased	41.40±0.81	43.60±0.76	46.20±0.65
Body weight gain(g)	Control	NA	3.80±0.44	3.70±0.34
	Treated healthy	NA	3.30±0.30	3.50±0.43
	Treated diseased	NA	2.10±0.28	2.60±0.22
Feed intake)kg)	Control	1.25±0.11	1.80±0.08	2.20±0.08
	Treated healthy	1.35±0.11	1.69±0.13	2.15±0.08
	Treated diseased	0.68±0.07	1.25±0.11	1.69±0.07

Bacteriological Identification

Microscopic examination of the bacterial samples revealed the presence of Gram-negative short rod or coccoid bacteria (0.2–0.4×0.6–2.5 µm in size), encapsulated, nonmotile, non-spore-forming. This aligned perfectly with *Pasteurella multocida*. Culturing the samples on blood agar further supported this identification, as the colonies displayed characteristics typical of *Pasteurella* spp., such as a gray, translucent, and non-hemolytic appearance. Additionally, other colonies on the blood agar exhibited features suggestive of *Streptococcus* spp., including grayish-white discoloration, smooth and glossy appearance, and zones of α/β-hemolysis. Microscopic examination confirmed the presence of coccoid Gram-positive bacteria without motility or spore formation. These cocci measured 0.5 to 2 µm in diameter. Some colonies surrounded by zones of clear beta-hemolysis indicated the presence of another type of Gram-positive bacteria, appearing as small, round (cocci) clusters resembling grapes (fig. 1).

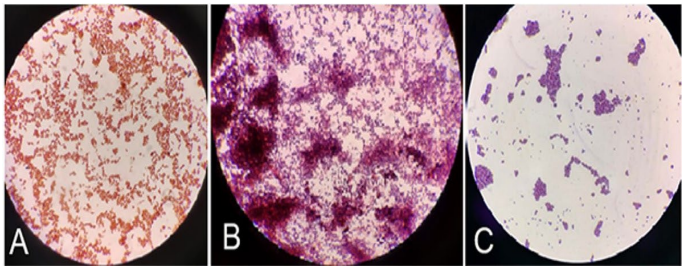

Fig. 1. Morphological characterization of *Pasteurella multocida* (A), *Streptococcus* spp. (B) and *Staphylococcus aureus* (C).

The identification of the bacterial isolates was further supported by biochemical characterization. The retrieved *P. multocida* isolates tested positive for oxidase, catalase, nitrate reduction, and indole, while they tested negative for urease, gelatinase, methyl red, and Voges-Proskauer tests. The recovered *Streptococcus* isolates tested negative for oxidase, catalase, and urease. The recovered *S. aureus* isolates, on the other hand, tested positive for coagulase, catalase, and nitrate reduction, but negative for urease and oxidase tests.

Results of the histological examination

lung sections of control groups (I&II) calves showed clear alveolar space, normal thickening of the alveolar septa and normal lung architecture (Fig. 2A). Moreover, Masson's trichrome stained sections showing ordinary amount of collagen fibers in the wall of the bronchioles and bronchial blood vessels also, minimal amount was observed in the interalveolar septa (Fig. 2F). On the other hand, the non-treated infected calves' lungs revealed sever lesions of fibrinous bronchopneumonia together with focal areas of red hepatization. Marked infiltration of red blood cells, neutrophils, and fibrinous exudates were demonstrated in the alveolar lumen (Fig. 2C) with marked thickening of the alveolar septa with lymphocytic infiltration within and around the alveoli and the bronchioles (Fig. 2C and D). Masson's trichrome stained sections showed fibrosis demonstrated by the blue stained collagen fibers deposition around the bronchioles and among the lung parenchyma (Fig. 2G and H). Pleural thickening with fibrin and cellular infiltration were noticed. Eosinophilic proteinaceous edematous substances were filling the respiratory bronchioles (Fig. 2B) and multifocal irregularly shaped areas of coagulation necrosis were detected in the lung parenchyma (Fig. 2D). Congestion of the bronchial blood vessels also noticed (Fig. 2D).

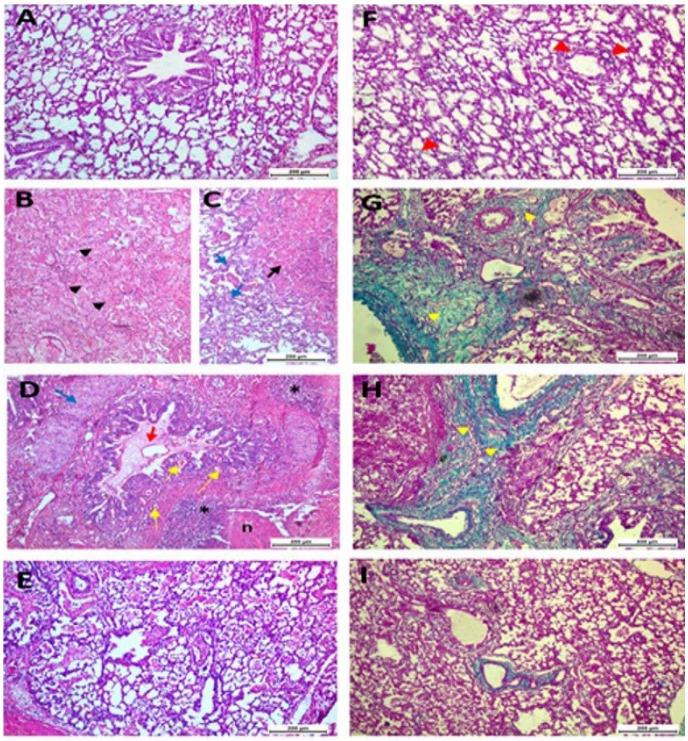

Fig. 2. Histopathological examination of H&E-stained sections of the lung tissue from the control group (A) showing clear alveolar space, normal thickening of the alveolar septa, normal lung architecture. While, Lung tissues from calves of the infected group (B, C and D) showing marked infiltration of red blood cells and neutrophils (black arrow), and fibrinous exudates (black head arrow) within the alveolar lumen, marked thickening of the alveolar septa (blue arrow), lymphocytic infiltration within and around the alveoli and the bronchioles (asterisk), the respiratory bronchioles filled with eosinophilic proteinaceous substances (red arrow), presence of multifocal irregularly shaped areas of coagulation necrosis (n) and congestion of the bronchial blood vessels appeared in the lung parenchyma (yellow arrows). Sections of the treated diseased group's lung (E) showing infiltration of macrophages into the alveolar lumen with normal lung architecture while presence of some fibrin-filled alveoli distributed within the lung parenchyma. Masson's trichrome staining of the control group lung (F) showed minimal distribution of collagen fibers in the wall of the bronchioles and bronchial blood vessels (red head arrow). While stained sections of the infected calves' lung (G and I) showed fibrosis and dense deposition of blue stained collagen fibers around the bronchioles and among the lung parenchyma (yellow head arrows). On the other hand, the lung of treated group sections (H) showed mild fibrosis around some bronchioles, while others had normal collagen fibers deposition around their wall.

Lung sections from treated group (III) showed infiltration of macrophages into the alveolar lumen that resulted in shrinkage and clearance of the fibrinous exudates from the alveolar lumen in many regions. Some areas still showed mild signs of inflammation and edema with normal architecture (Fig. 2E). In addition, mild fibrosis appeared in the Masson's trichrome stained sections around some bronchioles, while others showed normal

collagen fibers deposition around their wall (Fig. 2I) that indicates improvement in the pathological status following treatment with ceftiofur.

DISCUSSION

BRD is a contagious respiratory disease that affects cattle and has several diverse underlying causes, including serious bacterial infections like *Pasteurella multocida*. The pathogenesis of these bacteria is influenced by a number of variables, such as stress and possible viral or parasitic infections that frequently suppress the host immune system and allow these bacteria to proliferate swiftly in the upper respiratory tract (Griffin *et al*., 2010)

P. multocida infection prevention and treatment still mostly rely on antimicrobials (ferraro *et al*., 2020). One particular antibacterial agent that has been authorized in the USA is ceftiofur, a third-generation broad-spectrum cephalosporin. It is extensively used to treat respiratory conditions in cattle (Hornish and Kotarski, 2002).

Pretreatment clinical data evaluation, regarding body weight, body weight gain and feed intake data analysis revealed that there was significant decrease in the diseased group compared to the healthy groups at day 0. This agreed with numerous studies (Eckersall and Bell, 2010; Blakebrough-Hall *et al*., 2020). Animals may not develop normally and may not reach their genetic potential for growth and carcass value because of the inflammation brought on by BRD's activation of the inflammatory response (Eckersall and Bell, 2010).

Morrison *et al*. (2021); Costa *et al*., (2021) and Cantor *et al*. (2022) observed that Calves consumed less milk when a bout of BRD began compared to healthy calves. However, the present results disagreed with Cramer and Ollivett (2020) who reported that reduced milk intakes were noticed one day before diagnosis, so milk and calf starter consumption were not associated with BRD status. Cantor *et al*. (2022) believed that the diverse milk-feeding schedules adopted for the calves were the causes of the results variances. The present study showed that treated diseased group with ceftiofur showed improvement in the body weight, body weight gain and feed intake. It was reported that giving ceftiofur to birds did not have a negative impact on the birds' body weight growth. On the contrary, throughout the trial period and at various ages, the treated birds with ceftiofur sodium really gained more weight than the untreated birds (Chaudhry *et al*., 2013). This could be explained in view of the study conducted on poultry (De souza oro *et al*., 2023). When paired with ceftiofur hydrochloride, glutamine increased hatchability and intestinal mucosa repair, helping to maintain intestinal health and improvement the feed consumption (De souza oro *et al*., 2023). Another study reported that antibiotics regulate microbiota, reducing some bacteria while fostering the growth of others, improving body weight and weight gain (Choi *et al*., 2018).

The present study showed that no significant changes in the body weight, body weight gain and feed intake in the treated health group with ceftiofur compared to control. This agreed to a study reported by Costa *et al*. (2022) who proved that the use of ceftiofur didn't have any effect on the body weight of chicks when there had been correct management during broiler rearing.

With regard to body temperature, a significant elevation in the mean body temperature of calves in the diseased group compared to the healthy groups at day 0 and day 7 was observed. this comes in alignment to the fact that fever was most common in BRD calves (Kluger, 1991; ferraro *et al*., 2020). This could be explained on the bases of immunologic reactions taking place in response to the infection Inflammatory cytokines generated during infection trigger the development of fever (Kluger, 1991; ferraro *et al*., 2020).

It was also suggested that when the BRD data were analyzed independently, calves with fever had increased probabilities of having a depressed attitude, adding more proof that fever significantly affects attitude scores. (Kluger, 1991; ferraro *et al*., 2020).

At the beginning of the study the diseased animal showed sever signs of depression, mucopurulent to cloudy nasal discharge, sever ocular discharge, spontaneous to signal cough and bilateral ear position to head shake that regarded to the previous study of Ferraro *et al*. (2020); Cantor *et al*. (2021) and Cantor *et al*.(2022) who observed that when compared to healthy calves, BRD calves had higher lying times, fewer step counts, and lower acceleration activity index. This could be an example of illness behavior, in which activity is normally reduced to conserve energy for battling illness. Mucopurulent nasal discharge and ocular discharge were among the clinical symptoms that were like those seen in clinical instances of BRD by Toaff-Rosenstein *et al*. (2016). Nasal discharge was illustrated also by Griffin *et al*. (2010) who reported that loss of cilia is caused by primary infection of the epithelial cells lining the pharynx, trachea, and nasal cavity. The accumulation of fluid and cellular debris in the airways and alveoli, which is caused by impaired mucociliary clearance, created the perfect conditions for bacterial colonization.

Post-treatment clinical data evaluation, regarding body weight, body weight gain and feed intake recorded significant increase in the treated diseased group with 2mg / kg ceftiofur at day 14 compared to the 0 day. Body weight recorded on day 14 was 46.20 kg compared to 41.40 on day 0, body weight gain was 2.60 kg on day 14 compared to day 7 (2.10) and feed intake at day 14 was 1.69 compared to 0.68 on day 0. The depression, nasal, ocular discharge, cough, and ear score regarded disappear from the day 7 to completed recovery at day 14. The results related to Sreenivasa *et al*. (2018) which concluded that ceftiofur sodium can be effectively used in the treatment of bovine bacterial pneumonia. Also, following treatment with ceftiofur, nasal bacterial loads in sows and their offspring decreased, suggesting less bacterial transfer from the dams. The piglets' nasal microbiota composition also showed indications of dysbiosis. Another study reported that nebulizing sodium ceftiofur is a typical treatment for horses with lower respiratory tract bacterial infections because it is well tolerated (Fultz *et al*., 2015). The complete recovery of the diseased calves with no passive effect of the ceftiofur agree with the previous study of Vilos *et al*. (2014) who proved that ceftiofur is a strong candidate for biotechnological applications in the veterinary industry due to the sustained release of ceftiofur at a therapeutic level, the low toxicity, and the high antimicrobial efficacy.

Pasteurella multocida is the result of the bacteriological isolation study, and it was recognized using a variety of techniques, including a clinical examination in conjunction with bacterial isolation on selective media and histopathological lesions, all of which were useful in the early diagnosis of pasteurellosis (Amin, 2020). The present findings concur with earlier study of Scott (2013) and Sreenivasa *et al*. (2018) who reported that *Pasteurella multocida* was the most predominant bacteria caused the bovine respiratory disease.

The histopathological examination of study showed that lungs of the pretreated dead animals had lungs with lesions of fibrinous bronchopneumonia together with focal areas of red hepatization. Marked infiltration of red blood cells, neutrophils, and fibrinous exudates were demonstrated in the alveolar lumen with marked thickening of the alveolar septa with lymphocytic infiltration within and around the alveoli and the bronchioles. These histopathological changes may be due to *P. multocida* endotoxins and toxic proteins such as leukotoxin, lipopolysaccharide and polysaccharide (Hodgson, 2006) and due to the inflammatory factors produced by neutrophils and other inflammatory cells (Slocombe *et al*., 1985).

These findings were similar to observations made by earlier researchers, Griffin *et al*. 2010 approved that loss of cilia or necrosis of bronchial and bronchiolar epithelial cells is caused by primary infection of the bronchi and bronchioli. Primary infections that affect the epithelial cells in the trachea, bronchi, and alveoli caused necrosis of the ciliated epithelium. The mucociliary system's ability to adequately filter fluid, dust, and cellular debris from the airways was compromised by this condition,

Hodgins and Shewen (2004) illustrated that the most common cause of death in animals with BRD is acute pleuropneumonia. Lesions are referred to as serofibrinous pleuropneumonia. During necropsy, the lungs frequently showed bilateral consolidation and a thick, stiff texture. Oedema and a coating of yellow fibrin spread throughout the affected tissues. Also, Fulton *et al*. (2002) approved that coagulation necrosis is a condition that develops over time in infections that are chronic. Oedema, fibrin deposition, congestion, or bleeding in the alveoli are early warning signs that large-scale adhesions may form. Large-scale adhesions are also caused by the organization of fibrin deposits in the pleural and pericardial cavities. Interestingly, ceftiofur efficiently mitigated the *Pasteurella multocida* histopathological lesions in the diseased group therefore, improved the lung architecture and the clinical manifestations as well were noted.

CONCLUSION

A single sub cutaneous dose of ceftiofur at the level of 2mg/kg improved the body weight, body weight gain and feed intake in diseased animals in a short period of time (7 days). Thus, a single dose exhibits complete vanishing of any symptoms of BRD, as manifested by retaining normal attitude, body weight gain, feed intake, body temp., ear and cough scores, and lack of any discharges after 14 days and confirmed by histopathological findings. Nevertheless, ceftiofur had no negative impact on healthy animals regarding all measured parameters. Therefore, ceftiofur is to be recommended as a single subcutaneous antibiotic for treatment of common bovine respiratory disease in calves.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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