https://doi.org/10.52973/rcfcv-e34418 Revista Científica, FCV-LUZ / Vol. XXXIV, rcfcv-e34418

A field study on rational choice of medication: The use of Tilmicosin and Cefquinome in ovine footrot treatment

Un estudio de campo sobre la elección racional de la medicación: el uso de tilmicosina y cefquinoma en el tratamiento de la pododermatitis ovina

***Ferit Yıldız*[1]*, *Musa Gençcelep*[2]**

[1]*Provincial Directorate of Agriculture and Forestry. Muş, Türkiye.*
[2]*Van Yüzüncü Yıl University, Faculty of Veterinary, Department of Surgery.Van, Türkiye.*
**Corresponding author: ferit49@gmail.com, ferit.yildiz@tarimorman.gov.tr*

ABSTRACT

In veterinary medicine, it is extremely important to use drugs that will not put human health at risk. In the treatment of animal diseases, the preference of drugs that accumulate in muscle tissue (meat) and are excreted from the body with milk because they create low treatment costs poses a public health and food safety risk. Veterinarians and animal breeders should pay attention to the use of drugs that do not leave residues in animal foods in the treatment of diseases of animals whose meat is eaten. With this study, it was aimed to reveal the healing time of Tilmicosin, which passed to milk and Cefquinome, which is not passed to milk are used in the treatment of footrot, especially in sheep raised for meat and milk, and what are the costs (medicine, labor, etc.) of both drugs to animal owners. The study was conducted on 80 sheep with footrot from sheep raised in Muş, Türkiye in 2020-21. As a result of field observations, anamnesis and clinical examinations, sheep with footrot were divided into two groups in equal numbers. One group was administered Cefquinome (1 mL·50 kg^{-1} im. every 24 hours –h–, 3 applications), while the other group was administered Tilmicosin (1 mL·30 kg^{-1} sc. 48 h later, 2 applications) and the animals were observed for 10 day (d). In the Cefquinome group, footrot could be treated at a rate of 90% on the 4th d and did not bring additional costs to the animal owners. It has been concluded that Cefquinome should be preferred in treatment in terms of animal health, food safety and public health due to its high treatment success, easy application in pasture conditions, and the availability of milk during treatment.

Key words: Antibiotic; food safety; footrot; residue; sheep

RESUMEN

En medicina veterinaria, es extremadamente importante utilizar medicamentos que no pongan en riesgo la salud humana. En el tratamiento de enfermedades animales, la preferencia por los medicamentos que se acumulan en el tejido muscular (carne) y se excretan del cuerpo con la leche porque crean bajos costos de tratamiento plantea un riesgo para la salud pública y la seguridad alimentaria. Los veterinarios y criadores de animales deben prestar atención al uso de medicamentos que no dejen residuos en los alimentos de origen animal en el tratamiento de enfermedades de los animales cuya carne se consume. Con este estudio, se pretendió revelar el tiempo de curación de la Tilmicosina, que pasa a la leche y el Cefquinome, que no se pasa a la leche que se utilizan en el tratamiento de la podredumbre de los pies, especialmente en ovejas criadas para carne y leche, y cuáles son los costos (medicamentos, mano de obra, etc.) de ambos medicamentos para los dueños de los animales. El estudio se llevó a cabo en 80 ovejas con podredumbre de ovejas criadas en Muş, Türkiye, en 2020-21. Como resultado de las observaciones de campo, la anamnesis y los exámenes clínicos, las ovejas con podredumbre se dividieron en dos grupos en igual número. A un grupo se le administró Cefquinoma (1 mL·50 kg^{-1} i.m. cada 24 horas –h–, 3 aplicaciones), mientras que al otro grupo se le administró Tilmicosina (1 mL·30 kg^{-1} s.c. 48 h después, 2 aplicaciones) y los animales fueron observados durante 10 días (d). En el grupo Cefquinome, la podredumbre del pie se pudo tratar a una tasa del 90 % en el 4º d y no supuso costes adicionales para los propietarios de los animales. Se ha llegado a la conclusión de que el cefquinomo debe ser preferido en el tratamiento en términos de sanidad animal, inocuidad de los alimentos y salud pública debido a su alto éxito en el tratamiento, su fácil aplicación en condiciones de pasto y la disponibilidad de leche durante el tratamiento.

Palabras clave: Antibiótico; seguridad alimentaria; pododermatitis; residuo; oveja

Received: 13/03/2024 Accepted: 24/04/2024 Published: 25/07/2024

INTRODUCTION

Footrot, is the most common and contagious foot disease in small ruminants with main factor *Dichelobacter nodosus* and causes significant yield losses in sheep (*Ovis aries*) breeding [1, 2, 3]. The severity of the disease varies depending on factors such as sensitivity of the animal, environmental conditions and farm practices. Footrot, causes severe pain and lameness in the affected animals [3]. It is usually characterized by hoof deformation, foul interdigital skin smelling; necrotic-ulcerative dermatitis and inflammatory reactions spread towards the deep layers of the nail (FIG. 1) [4].

FIGURE 1. Erosive-ulcerative lesion (*) in the interdigital region and deformations (arrows) are observed in the surrounding areas

In addition to the decrease in meat, milk and wool yield, it causes significant economic losses as it reduces fertility, lamb growth rates and the opportunities of animal sales in infected farms. Therefore, footrot is a serious animal welfare problem in sheep-raising countries [5, 6, 7].

Various antibiotics such as Penicillin, Streptomycin, Lincomycin, Spectinomycin, Oxytetracycline, Tylosin and Erythromycin were used alone or in combinations by parenteral route for footrot treatment. In addition, antiseptics such as Zinc Sulphate, Copper Sulphate and Formalin were applied in the bath style [8, 9, 10, 11]. It has been reported that Penicillin-Streptomycin, Amoxicillin, Tilmicosin and long-acting Oxytetracyclines should be used in the treatment of animals with severe lesions [3, 11, 12]. Many researchers suggested that practices such as regular nail cutting, foot baths, antimicrobials, vaccination, quarantine and decommissioning should be applied together for the treatment, control and eradication of footrot [3, 12, 13]. As stated in a study conducted in Muş and its region, due to the humid environments in the province of Muş, which is located in the east of Türkiye and receives a significant amount of rainfall in three seasons of the year except for the summer months, piyeten, which is the most important foot disease of small ruminants, was detected at a rate of 9.14%, but it was seen that the breeders did not have enough information about its treatment [4]. In this investigation in the Muş plain it was found that some of the breeders applied substances like tar to cover only the wound on the feet for the treatment of footrot in field and herd scans. It has also been observed that most of the breeders used long-acting (LA) parenteral antibiotics without knowing that they should not have consumed milk and meat for a certain period of time after using antibiotics; they were unaware of the Drug Residue Clearance Time (DRCT); and those who knew the subject did not care much has been observed.

The unconscious and abusive use of antibacterial drugs creates serious economic and public health problems. For this reason, it has been reported that necessary measures should be taken to prevent these negative effects [14, 15]. The uncontrolled use of antibacterial drugs in this way does not only cause damage to human and animal health and the environment, especially to foods obtained from animals but also brings an additional burden to the country's economy [16]. Depending on the consumption of foods containing antibiotic residues, the danger of superinfection in humans, changes in the bacterial flora of the small and large intestine, teratogenic, carcinogenic and mutagenic effects may be observed [17, 18, 19, 20].

It has been understood that we are facing a serious problem for food safety, public health and animal health due to the fact that the meat and milk produced by the breeders enter the food chain without waiting for DRCT.

In this study; In the treatment of footrot disease, which occurs in sheep raised especially for meat and milk in Muş province, Türkiye, it is aimed to ensure rational drug use and to protect animal health, as well as food safety and public health, by comparing the success rates of two antibiotics whose residues and excretion from the body are done through different systems.

MATERIALS AND METHODS

This study was carried out on 80 mature Morkaraman-Akkaraman sheep in small ruminant farms engaged in pasture-based rearing in Muş. The sheep with footrot problems included in the study were determined based on anamnesis and clinical examinations during the pasture period.

Two different antibiotics with different mechanisms of action were used for the treatment of footrot. These are:

A. Cefquinome (Cefalosporin group antibiotic): According to the drug prospectus; it does not pass into milk and leaves a short-term (5 days –d–) residue in meat. 50 mg·mL^{-1} cefquinome.

B. Tilmicosin (Macrolide group antibiotic): According to the drug prospectus; it leaves residue in milk for 15 d (30 milking) and 42 d in meat. 300 mg·mL^{-1} Tilmicosin.

A certificate was obtained from the Ministry of Agriculture and Foresty that there was no need for an ethics committee approval certificate for the animals used in this study.

Foot rot is typically classified by most countries based on the prevalence and severity of clinical foot lesions using a different scoring system or a modification of the Swiss scoring system. In this study, since it would be very difficult to score and control the lesions on all feet of 80 sick animals in different flocks every day, sheep with foot rot and lesions on their feet based on clinical examination, which is a more practical way in field conditions, were classified according to the

lameness classification of Samsar *et al.* [21]. Accordingly; 1 -No Lameness, 2 –Mild Lameness: Lameness is imperceptible, 3 –Moderate Lameness: There is no noticeable abnormality when standing, but a more or less obvious dysfunction is seen in walking and trotting, 4 –Severe Lameness: The animal cannot step on the sick foot at all or this foot crawls on the ground. The movement is mostly done on three legs and by hopping.

The sheep with footrot in the farms/herd were divided into two groups with equal numbers; both drugs were applied under field conditions or in the sheep's own farm; and the care and feeding differences between the groups were eliminated. Sheep with 3-Moderate and 4-Severe lameness degrees were included in the created treatment groups. The head and tail parts of the sheep in the treatment groups were painted in different colors so that they can be easily found in the herd and the following antibiotics were applied at the specified dose and duration, and the treatment process of the disease was followed for 10 d. The recovery data obtained were recorded and evaluated statistically.

1. S-Group (Cefquinome Group – 40 animals): The drug was used intramuscularly at a dose of 1 mg·kg^{-1} (1 mL·50 kg^{-1} as a practical dose, repeated every 24 h). Due to its toxicity, a maximum of 5 applications were made and the animals were observed for 10 d.
2. T-Group (Tilmicosin Group – 40 animals): 10 mg·kg^{-1} of the drug was administered subcutaneously (1 mL·30 kg^{-1} as practical dose, to be repeated 48h later). To avoid toxicity, a maximum of two applications were made and the animals were observed for 10 d.

Statistical analysis

In this study, the Power (Test Power) was determined by taking at least 0.80 and Type-1 Error 0.05 in calculating the sample width (size). Descriptive statistics for the variables in the study were expressed as Mean, Standard Error, Number (n) and Percent (%). Shapiro-Wilk (n<50) and Skewness-Kurtosis tests were used to determine whether the continuous measurement averages were normally distributed, and because the variables were normally distributed, Parametric tests were applied. Independent T-test was calculated to compare the mean of measurements according to the groups. ANOVA was used in repeated measurements to compare the measurements according to the measurement times (days) separately in the groups. "Bonferroni Post-Hoc (Multiple) Comparison Test" was used to determine the days that made up the difference following the Repeated ANOVA. The statistical significance level (α) was taken as 5% in the calculations, and the SPSS (IBM SPSS for Windows, ver. 24) statistical package program was used for the calculations. The follow-up status of the patients in the T and S groups with regard to lameness is also shown graphically.

RESULTS AND DISCUSSIONS

Clinical results

The conditions of the diseased animals before the treatment and during 10 d of follow-up period were shown in the TABLE I.

At the end of the first 24h (d 1), there was no sign of improvement in both groups, while at the end of the second day there was an improvement of 12.50% in the T–Group and 50% in the S–Group. After the 3rd d, it can be seen that the recovery values of both groups are close to each other. At the end of the 4th d, an improvement of 85-90% was observed in both groups, and at the end of the 6th d, this rate increased to 90-95%. At the end of the 10th d, full recovery was observed in the S–Group, while there were still unhealed animals in the T–Group (TABLE I).

TABLE I
Table of percentages (%) of recovery of sheep in groups T and S during 10 days of follow-up period

Days	T–Group (n=40)	S–Group (n=40)
Before application	0	0
1	0	0
2	12.5	50.0
3	60.0	77.5
4	85.0	90.0
5	87.5	90.0
6	90.0	95.0
7	90.0	95.0
8	90.0	95.0
9	92.5	97.5
10	92.5	100

Statistical data

As indicated in TABLE II, there was a statistically significant difference (P<0.001) only on the 2nd d between the two groups, and no statistical difference was found on the other d (P>0.05). This situation is shown graphically in FIG. 2, and it was observed that the degree of lameness between the two groups was close to each other almost every day except the 2nd d, and the degree of the disease decreased significantly from severe to mild gradually.

TABLE II
Comparison of lameness degree by days and groups.

	S–Group (n: 40)	T–Group (n: 40)	*P***
	Mean±SEM	Mean±SEM	
Before application	3.85±0.06^{aA}	3.80±0.06^{aA}	0.562
Day 1	3.03±0.09^{bA}	3.00±0.09^{bA}	0.850
Day 2	1.65±0.12^{cB}	2.28±0.12^{cA}	**0.001**
Day 3	1.30±0.10^{cA}	1.50±0.11^{dA}	0.182
Day 4	1.18±0.09^{cA}	1.23±0.09^{dA}	0.704
Day 5	1.18±0.09^{cA}	1.20±0.09^{dA}	0.847
Day 6	1.13±0.09^{cA}	1.18±0.09^{dA}	0.689
Day 7	1.15±0.10^{cA}	1.18±0.09^{dA}	0.855
Day 8	1.10±0.07^{cA}	1.18±0.09^{dA}	0.503
Day 9	1.03±0.03^{cA}	1.15±0.08^{dA}	0.159
Day 10	1.00±0.00^{cA}	1.15±0.08^{dA}	0.079
P*	**0.001**	**0.001**	

*: Significance levels according to ANOVA Test results in repeated measurements. ^{a,b,c,d}: Different lowercase letters in the same columns indicate a statistical difference between days according to Bonferroni Post Hoc multiple comparison test. **: Significance levels of the difference between groups according to Independent T-test results. ^{A,B}: Different uppercase letters in the same rows indicate a statistical difference between groups. SEM: Standard Error of Mean

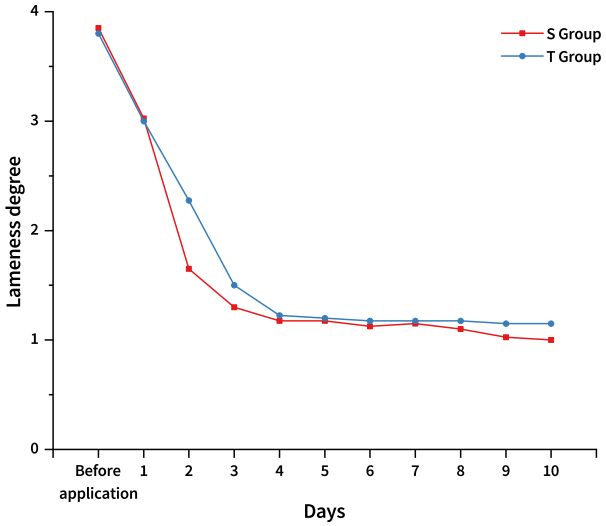

FIGURE 2. Control chart of lameness degree of sheep in T and S Groups (10 d)

Footrot disease is contagious disease and can infect healthy animals when left untreated or detected late. In regions where pasture husbandry is common the disease can be transmitted to the herd at any time as the pastures are contaminated, and it means an undeniable loss of income in sheep breeding.

The incidence of the disease varies according to the regions depending on the predisposing conditions. Sağlıyan [22] reported that the incidence of footrot was 18.95% in his study in the Elazığ region, and in another study conducted in the Eastern Anatolian Region the incidence of the disease was found to be 8.3% in Malatya, 15.4% in Elazığ and 9.1% in Bingöl [17]. Yıldız and Gençcelep [4] reported that the incidence of footrot was 9.14% in Muş region.

Animal welfare is a major concern in today's society. In sheep breeding one of the main animal welfare problems is footrot [23]. Forbes *et al.* [24] reported successful results in the treatment of the entire herd with antimicrobials in the elimination of the disease, and Strobel *et al.* [25] reported recovery rates of more than 99% after one or two systemic antimicrobial applications. Whittington [26] stated that antibiotics should be used for a long time for the treatment of footrot and must remain at the therapeutic level for at least 18 h to be effective.

In this study, the effectiveness of antibiotics in the treatment of footrot was demonstrated, and a treatment success rate of over 90% was observed after 2-3 applications. In this respect, it is consistent with the findings of Strobel *et al.* [25]. In the study, a significant treatment difference (12.5 – 50%) was detected between the T and S groups, especially on the 2nd d, and this is thought to be due to the application of the second dose of Tilmicosin after 48 h and the repetition of cefquinome after 24 h. As a matter of fact, Whittington [26] supports this situation with the determination that antibiotics must remain at therapeutic doses for at least 18 h in order to be effective.

Casey and Martin [27] reported that with the intramuscular aplication of the combination of Penicillin + Streptomycin and the application of 10% $CuSO_4$ solution as bath, recovery can be achieved within three months. Gönül *et al.* [28] reported that the combination of Penicillin + Streptomycin was 92% successful with parenteral application of 5% Copper Sulfate ($CuSO_4$) solution as bath. Bruere and West [29], also reported that they were 90% successful in their application by keeping it in a 10% $ZnSO_4$ bath for 5 minutes with the combination of Penicillin + Streptomycin. In their study conducted in Muş and its surrounding, Yıldız and Gençcelep [4] reported that they achieved 90% recovery rate by applying Ceftiofur + Flunixin Meglumine to the sheep with footrot, and they saw this medication choice as an advantageous treatment option in terms of eliminating the need for milk disposal. Karslı and Elma [30] also stated that the application of Zinc Sulfate ($ZnSO_4$) footbath, which they use alone as an antiseptic, is insufficient in the treatment, but the application of Zinc Sulfate ($ZnSO_4$) footbath together with parenteral Spiramycin and vitamin E application is more effective in the treatment. Greber *et al.* [13] and Kraft *et al.* [31] stated in their studies that a single macrolide combined with footbath in an infected herd can treat the entire herd and eliminate the footrot disease and its causative agent (*D. nodosus*). As mentioned above, many researchers have tried to treat footrot with different treatment options, but treatment options have always been supported by an antibiotic agent and it has been observed that foot baths or vitamin supplements are not sufficient. As a matter of fact, Yarsan [32] mentioned that residues in animal foods are an increasing global problem. Groenevelt and Grogono-Thomas [33] stated that a single antimicrobial agent significantly improves animal welfare in treatment, and it has been reported by many researchers that systemic antibiotics do not show any difference in the recovery of the disease [10, 11]. In this study, by applying two different antibiotics with different mechanisms of action to two different groups, the efficacy of antibiotic application alone was proven, and by making rational drug selection, the risk of residue, which is a very important problem, was eliminated without reducing the chance of treatment.

Scientists state that more than 131.000 tons of antibiotics were used in animals worldwide in 2013, and the projected consumption will exceed 200.000 tons by 2030, an increase of 53% [34]. Van Boeckel *et al.* [35], on the other hand, reported that the use of antibiotics in animal husbandry in the world far exceeds the amount of human use, and although there are no regularly recorded data on antibiotic use in some regions. Turkey is the country with the highest rate of antibiotic use in the world (47.86 daily dose per 1000 people) in human medicine [36]. Gülmez [37] reported that antibiotic resistance in Turkey has increased to 35%, but this rate has been reduced to 5% in some European countries. In veterinary medicine, there is no reliable data on the amount of use of veterinary drugs. It is reported by Yarsan [38] that this situation can be corrected by applying data matrix and creating traceability plans, especially in drugs. With this study, we tried to create an approach and awareness for veterinarians and animal breeders to make rational drug choices while treating their sick animals, taking into account the residue problem, and to protect human health.

Before implementing a footrot elimination program based on antimicrobials, it should be investigated whether strict biosecurity measures can be taken to avoid relapses, repetitive antimicrobial treatments and economic losses [31]. If antibiotics that pass into milk are used during the treatment process of footrot disease, it should not be used as human food for 10-30 milkings depending on the drug. Odabaşıoğlu [39] stated that the lactation period of Akkaraman sheep is 146.9 d; the milk yield is 73.6 kg, while the lactation period of the Morkaraman sheep is 167.2 d, and the total milk yield is 92.0 kg. Therefore, 500-550 mL (per sheep) of milk is taken daily from them during the lactation period, and when it is considered on a flock

basis, milk is an extremely valuable source of income for breeders. According to the information we received from the breeders during our study, it was determined that they did not look forward to the destruction of milk as it caused a serious loss of income in previous treatment attempts.

In the light of this information, in this study carried out in Muş and its region, where Morkaraman and Akkaraman sheep breeds are common, a treatment comparison was made between the preparation with Cefquinome active ingredient that does not pass into milk and the preparation with Tilmicosin which leaves residue in milk and meat for a long time so that the breeders use the milk with peace of mind and do not have to waste the milk.

It has been determined that both antibiotics are strong in terms of therapeutic efficacy and there is no significant difference between them. This is in line with the report by Venning *et al.* [10] and Winter [11] that systemic antibiotics do not differ in the recovery of the disease. In addition, in terms of treatment success it was observed that both drugs cured the disease by 90-95% after the 6^{th} d, and the success rates increased further in the following days. This situation is also consistent with the above-mentioned literature data on systemic antibiotics [4, 24, 25, 26, 27, 28, 29, 30].

In the market conditions of 2021, it is seen that the same dose of Cefquinome preparations are sold at the same price as Tilmicosin preparations or 20-30% more. As stated in the materials and methods section for drug use and dosage, Tilmicosin will be practically calculated according to 1ml/30kg body weight and a maximum of two applications can be made due to drug toxicity, and for Cefquinome, 3-5 applications can be made corresponding to 1 mL·50 kg^{-1} body weight. In our study, three applications were sufficient because over 90% treatment success was achieved after the third application of Cefquinome. The average live weight of the sheep included in the study groups was 50-55 kg, a total of 124 mL of Cefquinome was applied to the S-Group, and a total of 136 mL of Tilmicosin was applied to the T-Group. Therefore, since both drugs are very close to each other in terms of consumption and cost, there is no need to make an evaluation on this issue.

CONCLUSION

In conclusion, when planning treatment in animals raised for food purposes, rational drug selection should be made, taking into account the risk of drug residue. On this occasion, when the drug containing the active ingredient Cefquinome is used in the treatment of footrot disease with antibiotics, the success rate exceeds 90% after the 4^{th} d, it is capable of treating the disease in a short time with three applications, it does not require additional costs, it can be easily obtained by growers and it can be used easily in field conditions. It has been evaluated that it can be preferred by breeders as it does not pass into milk and does not pose a risk of residue and milk is not wasted. Thus, it was concluded that it should be recommended for both animal health and welfare, food safety and public health.

Financial support

This study was supported with the project code TSA-2020-8176 by the Presidency of Van YYU Scientific Research Project.

Conflict of interest

The authors declare that there are no conflicts of interest.

BIBLIOGRAPHIC REFERENCES

[1] Sağlıyan A, Güney C, Koparır M. [The Role of Copper and Zinc in the Etiology of Footrot of Sheep in Elazığ Region]. Vet. Cer. Derg. 2003; 9(1-2):11-16. Turkish.

[2] Sertkaya H, Şındak N. [Incidence and treatment with two different drug combinations of sheep's footrot in Birecik district of Şanlıurfa and its villages]. Vet. Cer. Derg. 2004; 10(1-2):48-54. Turkish

[3] Sulu K, Alkan F. [Footrot]. Bahri Dağdaş Hayvancılık Araştırma Dergisi. [Internet]. 2018 [cited 12 Feb 2024]; 7(1):18-32. Turkish. Available in: https://goo.su/W0UML

[4] Yıldız F, Gençcelep M. [Comparative Studies on the Treatment and Incidence of Footrot in Sheep in Muş and its Region]. Van. Vet. J. [Internet]. 2021; 32(1):33-42. Turkish. https://doi.org/m84f

[5] Green L, Kaler J, Wassink G, King E, Grogono-Thomas R. Impact of rapid treatment of sheep lame with footrot on welfare and economics and farmer attitudes to lameness in sheep. Anim. Welf. [Internet]. 2012; 21(S1):65-71. https://doi.org/f3zh2q

[6] Lovatt F. Causes, control and costs of lameness in sheep. Vet. Irel. J. [Internet]. 2015 [cited 12 Jan 2024]; 5(4):189-192. Available in: https://goo.su/1ZVnow

[7] Wassink GJ, King EM, Grogono-Thomas R, Brown JC, Moore LJ, Green LE. A within farm clinical trial to compare two treatments (parenteral antibacterials and hoof trimming) for sheep lame with footrot. Prev. Vet. Med. [Internet]. 2010; 96(1-2):93–103. https://doi.org/bx8z3v

[8] Abbott KA, Lewis CJ. Current approaches to the management of ovine footrot. Vet. J. [Internet]. 2005; 169(1):28-41. doi: https://doi.org/bcsw9s

[9] Grogono-Thomas R, Wilsmore AJ, Simon AJ, Izzard KA. The use of long-action oxytetracycline for the treatment of ovine footrot. Br. Vet. J. [Internet]. 1994; 150(6):561-568. https://doi.org/gf8f7j

[10] Venning CM, Curtis MA, Egerton JR. Treatment of virulent footrot with lincomycin and spectinomycin. Aust. Vet. J. [Internet]. 1990; 67(7):258-260. https://doi.org/cmb32k

[11] Winter A. Lameness in sheep. Small. Rum. Res. [Internet]. 2008; 76(1-2):149-153. https://doi.org/bbnk67

[12] Alkan F. [Foot diseases in sheep and general approach]. In: 3rd Sheep Goat Health and Management Congress; 27-29 Apr 2017; Bursa (Türkiye): Farm Animal Medicine Association; 2017. p 23-32. Turkish.

[13] Greber D, Bearth G, Lüchinger R, Schüpbach-Regula G, Steiner A. Elimination of virulent strains *(aprV2)* of *Dichelobacter nodosus* from feet of 28 Swiss sheep flocks: a proof of concept study. Vet. J. [Internet]. 2016; 216:25-32. https://doi.org/f87qw5

[14] O'Neill J. Tackling drug-resistant ınfections globally: Final report and recommendations. The review on antimicrobial resistance [Internet]. London: Government of the United Kingdom; 2016 [cited 05 Feb 2024]; 84 p. Available in: https://goo.su/RTnHz

[15] European Centre for Disease Prevention and Control. Guidelines for the prudent use of antimicrobials in veterinary medicine. Off. J. Eur. Union [Internet]. 2015 [cited 18 Feb 2024]; 26 p. Available in: https://goo.su/inGyzP

[16] World Health Organization. Regional Office for Europe. Tackling antibiotic resistance from a food safety perspective in Europe [Internet]. Geneva (Switzerland); World Health Organization. Regional Office for Europe; 2011. 65 p. Available in: https://goo.su/gJLRVe

[17] Bulut S. Elazığ ve yöresi koyun ve keçilerde görülen Piyeten'in etiyoloji, klinik seyir, epidemiyolojisi ile sağıtımlarının karşılaştırmalı araştırması [Comparative research on the etiology, clinical course, epidemiology and treatments of Piyeten seen in sheep and goats in Elazığ and its region]. [dissertation on the Internet]. Elazığ (Türkiye): Firat University; 1982 [cited 7 Sep 2023]. 110 p. Turkish. Available in: https://goo.su/6VpuIC

[18] Klimek L, Aderhold C, Sperl A, Trautmann A. Allergic reactions to antibiotics – two sides of the same coin: clearly diagnose or reliably rule out. Allergo J. Int. [Internet]. 2017; 26:212-218. https://doi.org/m84g

[19] Schenck FJ, Callery PS. Chromatographic methods of analysis of antibiotics in milk. J Chromatogr A. [Internet]. 1998; 812(1-2):99-109. https://doi.org/c6cj9f

[20] Tadesse T, Tadesse T. Public health impacts of antibiotic residues in foods of animal origin: A review. Public Policy Adm. Res. [Internet]. 2017 [cited 21 Feb 2024]; 7(10):6-11. Available in: https://goo.su/3gelJ7

[21] Samsar E, Akın F, Anteplioğlu H. Klinik Tanı Yöntemleri ve Genel Cerrahi [Clinical Diagnosis Methods and General Surgery]. 6th ed. Ankara (Türkiye): Tamer Matbaacılık Yayıncılık; 1996; 952 p. Turkish.

[22] Sağlıyan A. [Clinical Evaluation of Sheep Foot Diseases Observed in Elazığ Region]. FÜ Sağlık Bilimleri Dergisi. [Internet]. 2003 [cited 12 Feb 2024]; 17(1):39-44. Turkish. Available in: https://goo.su/Ds2c0ky

[23] Liu N, Kaler J, Ferguson E, O'Kane H, Green L. Sheep farmers' attitudes to farm inspections and the role of sanctions and rewards as motivation to reduce the prevalence of lameness. Anim. Welf. [Internet]. 2018; 27(1):67-79. https://doi.org/gc5px4

[24] Forbes AB, Strobel H, Stamphoj I. Field studies on the elimination of footrot in sheep through whole flock treatments with gamithromycin. Vet. Rec. [Internet]. 2014; 174(6):283-284. https://doi.org/gf8f6t

[25] Strobel H, Lauseker M, Forbes AB. Targeted antibiotic treatment of lame sheep with footrot using either oxytetracycline or gamithromycin. Vet. Rec. [Internet]. 2014; 174(2):46. https://doi.org/gbffmv

[26] Whittington RJ. Observations on the indirect transmission of VFR in sheep yards and its spread in sheep on unimproved pasture. Aust. Vet. Journal. [Internet]. 1995; 72(4):132-134. https://doi.org/dzhntc

[27] Casey RH, Martin PAJ. Effect of foot paring of sheep affected with footrot on response to zinc sulphate/sodium lauryl sulphate foot bathing treatment. Aust. Vet. Journal. [Internet]. 1988; 65(5):258-259. https://doi.org/dgwv4x

[28] Gönül R, Or ME, Dodurka HT. [Treatment of foot foot disease in sheep with penicillin+streptomycin combination and/or copper sulphate foot bath under field conditions]. İ. Ü. Vet. Fak. Derg. 2001; 27(1):171-177. Turkish.

[29] Bruere AN, West DM. The Sheep: Health, Disease and Production. Auckland (New Zealand): New Zealand Veterinary Association; 1993. Chapter 11, Foot diseases and lameness; p. 224-230.

[30] Karslı B, Elma E. [The Evaluation of the Efficacy of Different Treatment Methods for Virulent Footrot in Sheep]. Türkiye Klinikleri J. Vet. Sci. [Internet]. 2015; 6(2):39-47. Turkish. https://doi.org/m85d

[31] Kraft AF, Strobel H, Hilke J, Steiner A, Kuhnert P. The prevalence of *Dichelobacter nodosus* in clinically footrot-free sheep flocks: a comparative field study on elimination strategies. BMC Vet Res. [Internet]. 2020; 16(21). https://doi.org/m84h

[32] Yarsan E. Hayvansal Gıdalarda Veteriner İlaç Kalıntıları. In: Uluslararası II. Helal ve Sağlıklı Gıda Kongresi; 07-10 Nov 2013; Konya, Turkey. [cited 08 Sep 2023]. Available in: https://goo.su/Ehhhhz

[33] Groenevelt M, Grogono-Thomas R. What is the evidence base for blanket antibiotic therapy in the control of footrot in sheep? Livest. [Internet]. 2018; 23(Suppl. 5):20-23. https://doi.org/m84j

[34] Zanolari P, Dürr S, Jores J, Steiner A, Kuhnert P. Ovine footrot: A review of current knowledge. Vet. J. [Internet]. 2021; 271:105647. https://doi.org/m84k

[35] Van Boeckel TP, Glennon EE, Chen D, Gilbert M, Robinson TP, Grenfell BT, Levin SA, Bonhoeffer S, Laxminarayan R. Reducing antimicrobial use in food animals. Science. [Internet]. 2017; 357(6358):1350-1352. https://doi.org/ggqsht

[36] Klein E, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, Goossens H, Laxminarayan R. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc. Natl. Acad. Sci. USA. [Internet]. 2018; 115(15):E3463-E3470. https://doi.org/gc6x2n

[37] Gülmez M. [Antimicrobial Resistance: A Global Problem]. Dicle Üniv. Vet. Fak. Derg. [Internet]. 2022 [cited 21 Jan 2024]; 15(1):53-58. Turkish. Available in: https://goo.su/42t9Ur

[38] Yarsan E. Veteriner Hekimlikte Antibiyotikler (Pratik Bilgiler Rehberi) [Antibiotics in Veterinary Medicine (Practical Information Guide)]. Ankara (Türkiye): Güneş Tıp Kitapevleri; 2013. 280 p. Turkish.

[39] Odabaşıoğlu F. Morkaraman, Akkaraman ve İvesi Koyunlarının Süt Verim Özelliklerinin Karşılaştırılması [Comparison of Milk Yield Characteristics of Morkaraman, Akkaraman and Awasi Sheep] [dissertation on the Internet]. Elazığ (Türkiye): Firat University; 1983 [cited 7 Sep 2023] 58 p. Turkish. Available in: https://goo.su/w20NXr