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Risk factors associated with outcome in goats with encephalitic listeriosis: A retrospective study of 36 cases from 2008 to 2021

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Abstract

Background: There exists a scarcity of information on risk factors associated with case outcomes in goats diagnosed with encephalitic listeriosis.

Objective: Evaluate risk factors associated with outcomes in 36 cases of suspected encephalitic listeriosis in goats presented to a referral hospital.

Animals: Thirty-six goats (26 does, 7 bucks, and 3 wethers) were presented to Auburn University Large Animal Teaching Hospital between 2008 and 2021 for treatment of neurologic disease diagnosed as encephalitic listeriosis based on any combination of clinical signs, cerebral spinal fluid (CSF) analysis, or postmortem examination.

Methods: Retrospective study. Data were analyzed as binary and under a proportional odds model. The medical records were searched for presumptive encephalitic listeriosis in goats between 2008 and 2021. Data collected included signalment (sex, age, and breed), history, clinical signs, temperature, and ability to stand at presentation. Final diagnosis, CSF results, all treatments, outcomes, and results of necropsy were also collected for analysis.

Results: Male goats were 14 (95% CI: 1.98-166.0) times more likely to be a non-survivor compared to females despite being presented with similar history, clinical signs, and treatments. Animals presented with circling or a history of circling were 6.24 (95% CI: 1.40-23.21) times more likely to be a survivor than a non-survivor. Other risk factors evaluated were not significantly associated with outcomes.

Conclusions and Clinical Importance: Few risk factors were associated with outcomes. Duration of clinical signs, antimicrobial or anti-inflammatory choices, or CSF results were not associated with outcome. Only sex and history or presence of circling were associated with case outcomes.

KEYWORDS
encephalitic listeriosis, goat, *Listeria monocytogenes*, outcome

Abbreviations: CSF, cerebral spinal fluid; ICHH, immunocompetence handicap hypothesis; LM, *Listeria monocytogenes*.

1 | INTRODUCTION

Encephalitic listeriosis, also referred to as neurolisteriosis, is a common neurologic disease of ruminants, particularly of small ruminants such as sheep and goats.[1] This disease is caused by *Listeria monocytogenes* (LM) or less commonly, *Listeria ivanovii*. Both bacteria are Gram-positive that can cause various conditions including encephalitis. This bacterium is ubiquitous in the farm animal environment, and can be shed in many bodily fluids and feces by both apparently healthy carrier and clinically affected animals.[2] The bacterium is ingested and then crosses a break in the mucosal surface. *Listeria monocytogenes* travels centripetally through the axons of cranial nerves into the brainstem to cause rhomboencephalitis.[3] The microabscesses and inflammation lead to multifocal areas of necrosis and vasculitis, resulting in multifocal and asymmetric signs of brainstem dysfunction.[4–6] These might include unilateral cranial nerve deficits (commonly V-XII) resulting in facial hypoalgesia, drooping of the lip, eyelid, and ear, circling and/or head tilt toward the side of the lesion, dysphagia, and anorexia. Depression, recumbency, torticollis, and opisthotonos were often observed in more advanced cases.[7]

Although there exists a wealth of publications pertaining to the clinical signs, epidemiology of outbreaks, and transmission through milk, cheese products, or meat of small ruminants, there is a scarcity of studies evaluating the risk factors associated with case outcomes. Identifying factors associated with a favorable or unfavorable prognosis can guide small ruminant practitioners' decisions for goats diagnosed presumptively with encephalitic listeriosis.

The aim of this retrospective study was to determine if risk factors such as sex, history and physical exam findings, therapeutic interventions, or diagnostic results were associated with greater risk of non-survival.

2 | MATERIALS AND METHODS

2.1 | Case selection criteria

Medical records from Auburn University Large Animal Teaching Hospital (AULATH) were searched to identify goats that were treated for encephalitic listeriosis between March 2008 and July 2021. Search terms included caprine, LM—encephalitis/septicemia/other disease, listeriosis, encephalitis, inflammation—suppurative/meninges, diagnosis not in list, and pending diagnosis. Due to the medical record system utilized, case query could only be performed using diagnosis rather than individual nonspecific terms, thus cases with diagnosis not listed or pending diagnosis were also included in the initial search. Animals with the definitive or presumptive diagnosis of encephalitic listeriosis, no diagnosis listed but consistent clinical signs, or pending diagnosis following necropsy consistent with encephalitic listeriosis were further reviewed. Cases included in the analysis had to be presumptively diagnosed with encephalitic listeriosis based on signs including asymmetric cranial nerve deficits with or without ataxia, head tilt, or circling. Evidence of mononuclear or mixed cell pleocytosis increased suspicion of encephalitic listeriosis. Diagnosis of encephalitic listeriosis required 2 or more signs of neurologic disease if no cerebral spinal fluid (CSF) analysis was performed, 1 or more signs if consistent CSF results, or consistent lesions or culture positive on necropsy. Goats were excluded if necropsy revealed neurologic diseases other than or not in combination with listeriosis (eg, polioencephalomalacia, hepatic encephalopathy secondary to portosystemic shunt, or *Parelaphostrongylus sp*. infection).

2.2 | Medical records review

The following information was collected from each study-eligible case, if available: signalment (sex, age, and breed), history including duration of clinical signs before presentation/referral and first sign observed by owner. Factors at presentation such as clinical signs, temperature, and recumbency or standing were documented. Final definitive or presumptive diagnosis, CSF results, all treatments performed (class and total number of antibiotics, anti-inflammatory, neuroprotectants, and supportive therapies), outcome, survival or non-survival, and necropsy results were recorded. Survival was defined as survival to discharge and non-survival if the goat died naturally or was euthanized while admitted to the hospital.

2.3 | Statistical analysis

Descriptive statistics (mean ± SD, median, range, and 95% CI) were generated using a commercially available statistics program (GraphPad Prism version 9.3.1 for Windows, GraphPad Software, San Diego, California, USA, www.graphpad.com). Normality was assessed using D'Agostino and Pearson test. Chi squared or Fisher exact tests were employed to compare risk factors between survivors and non-survivors. Multiple logistic regression was used to determine the association of survival with risk factors with survival as the dependent variable. Duration of clinical signs, sex, circling, hypersalivation, recumbency, lethargy, anorexia, ataxia, and vestibular, facial, or trigeminal nerve dysfunction were set as the independent variables.

3 | RESULTS

Forty-three goats were treated for suspected encephalitic listeriosis at the AULATH during the study period. Seven goats were excluded from the study because of the determination of diseases other than encephalitic listeriosis on necropsy such as polioencephalomalacia (n = 2), hepatic encephalopathy secondary to portosystemic shunt (1), aberrant migration of *Parelaphostrongylus tenuis* (1), *Klebsiella* spp. septicemia (1), chronic spinal cord injury (1), and metabolic encephalopathy (1). Thus, only 36 goats were included in the final analysis. The study population included 8 Boer/Boer cross, 6 Pygmy, 5 Nubian/Nubian cross, 5 mixed breed, 2 Nigerian Dwarf, 1 Old Format Goat, and 9 goats of unspecified breeds. Included in the study were 26 intact

does, 7 intact bucks, and 3 castrated males (wethers). At the time of presentation for suspected neurologic disease, the study sample had a mean ± SD age of 2.6 ± 2.8 years (range, 0.12-12 years).

3.1 | Case history and physical exam findings

Duration of clinical signs before presentation or referral was recorded in 32/36 (89%) of cases. Mean time from first clinical sign noticed by the owner to presentation for survivors was 2.45 days (±2.76; 0.98-3.92) and 1.16 days (±0.79; 0.74-1.59) for non-survivors. The time was not significantly different between survivors or non-survivors (*P*-value .70). The first sign observed included circling 8/36 (22%), lethargy 7/36 (19%), stumbling/ataxia 7/36 (19%), head tilt 6/36 (17%), down 3/36 (8%), seizures 2/36 (6%), head pressing 1/36 (3%), regurgitation 1/36 (3%), and "neurologic" 1/36 (3%). Only 6/36 (17%) of cases were referred from a primary care veterinarian and 4/36 (11%) cases were treated by owners before presentation. One case had financial constraints preventing hospitalization, but appropriate medications were provided to the owner to treat the goat on farm. No case in the study had financial constraints that prevented treatment or necessitated euthanasia during treatment because of reaching financial limits.

At presentation, 21 goats were able to stand while 15 were recumbent (Table 1). Rectal temperatures were above 103.5°F in 17, 13 had rectal temperatures below 103.5°F, and for 6 the rectal temperature was not recorded. Of the recorded initial clinical signs, 28 had at least 1 cranial nerve deficit, 21 presented with a head tilt, circling at presentation or historically in 19 cases, and 14 were described as ataxic. Seven goats were anorexic, 3 showed opisthotonos, and 1 goat demonstrated head pressing. The history and physical exam findings were unavailable for 1 goat; thus, this goat was only included in the statistical analysis for treatments and outcome.

3.2 | Diagnosis

A presumptive diagnosis was made by the attending clinician based on history, clinical signs consistent with encephalitic listeriosis, and additional diagnostic tests such as CSF analysis. Consistent clinical signs included asymmetric cranial nerve deficits, head tilt, circling, and ataxia. Of the 36 goats presumptively diagnosed with encephalitic listeriosis, CSF analysis was performed in 24 animals. Mononuclear pleocytosis was the most common cytological finding in 11 cases with neutrophilic pleocytosis reported in 8 cases. Lymphocytic and eosinophilic pleocytosis were reported uncommonly in 4 and 1 cases, respectively. The goat with predominantly eosinophilic with secondary mononuclear pleocytosis was presumptively diagnosed and treated for *Parelaphostrongylus sp*. infection and encephalitic listeriosis. This goat demonstrated distinctive clinical signs of encephalitic listeriosis such as head tilt, circling, and dullness, but did not demonstrate characteristic clinical signs of *Parelaphostrongylus sp*. infection such as hind limb weakness or ataxia, thus was included in analysis.

TABLE 1 Odds ratios of risk factors observed between survivors and non-survivors.

Risk factor	Survivor	Non-survivor	*P*-value	Odds ratio	95% CI
Male	1	9	.01	0.07	0.006-0.51
Female	16	10			
Standing	11	11	.52	1.65	0.42-5.66
Recumbent	6	7			
Head tilt	12	9	.31	2.4	0.57-9.97
Head tilt absent	5	9			
Circling	12	5	.02	6.24	1.40-23.21
No circling	5	14			
Temp >103.5°F	7	12	.13	0.22	0.05-1.00
Temp <103.5°F	8	3			
Mono CSF	8	3	.24	…	…
Neutro CSF	3	5			
Lymph/Eos CSF	2	3			
Beta-Lactam	5	8	.36	…	…
Oxytetracycline	11	8			
Florfenicol	1	3			
Flunixin Meglumine	3	6	.35	…	…
Dexamethasone	13	8			
Both	2	2			
1 Abx	9	12	.74	0.66	0.19-2.63
≥2 Abx	8	7			

3.3 | Treatment

Interventions included antimicrobials in 36/36 (100%) and anti-inflammatory medications in 34/36 (94%) of cases (Table 1). These were often in conjunction with supportive care such as supplemental thiamine administration 23/36 (64%) and intravenous fluid therapy 7/36 (19%) of the study cases. Therapeutic protocols were clinician-dependent and were not consistent between each year of the study. Antimicrobial classes used during the study period included beta-lactams (procaine penicillin G, potassium penicillin, ceftiofur sodium, and ceftiofur crystalline free acid), oxytetracycline, and florfenicol. Beta-lactams were used as the first choice in 13/36 cases (36%), tetracyclines in 19/36 (53%), and florfenicol in 4/36 cases (11%). Antimicrobial classes were changed or added in 14/36 cases (39%) after an average of 57.9 hours (range, 12 hours-11 days). However, after removing the outlier of 11 days the average time was 42 hours (range, 12-72 hours).

The class and number of antimicrobials (1 or more changes in antimicrobial classes) used during treatment were not found to be statistically significantly associated with outcome in this study (*P*-value of .36 and .37, respectively; Table 1). Flunixin meglumine and dexamethasone, either alone or in combination were used for their anti-inflammatory effects in 34 of the 36 (94%) cases. Outcome was not significantly associated with choice of anti-inflammatory medication (*P*-value .35). Thiamine was added to the treatment regimen in 26 of 36 (72%) cases for its presumed neuroprotective effects and the prevention of polioencephalomalacia in anorexic animals.

3.4 | Outcome

Seventeen of the 36 animals survived to hospital discharge. Of these 17, owners of 5 animals provided follow-up information after discharge. Of those with follow-up information, 1 died shortly after being discharged from presumed relapse of encephalitic listeriosis and the other 4 returned to their herd with no further neurologic episodes. Risk factors significantly associated with outcome included sex and presence of circling at presentation. Of the surviving animals, 16 were does and only 1 was a buck (*P*-value .01) demonstrating a greater case fatality rate in males (Table 1). Of the survivors, 12/17 (71%) animals presented with circling or a history of circling with a *P*-value of .02.

Less than half, 7/15 (41%) of surviving animals were febrile at presentation with a rectal temperature greater than 103.5°F. Conversely, 12/15 (80%) of non-survivors were febrile at presentation ($P = .13$). Survivors that were standing and had a history of circling was not statistically significant compared to recumbent non-survivors without circling ($P = .05$; Figure 1). Recumbency, CSF findings, antimicrobial class and number, anti-inflammatory drugs used, presence of head tilt, or other cranial nerve deficits were not statistically associated with survival.

Nineteen of the 36 goats in the study did not survive to discharge. One goat died naturally during treatment and 18 were euthanized. Euthanasia was elected in 11 cases because of apparent lack of clinical improvement despite therapy and in 7 cases because of rapid deterioration of clinical signs. None of the cases were euthanized at presentation because of financial limitations. Of the non-survivors, 13 were submitted for necropsy to the Auburn University Department of Pathobiology. In all 13 cases, the clinical diagnosis of encephalitic listeriosis was confirmed by histology and/or bacterial culture. *Listeria monocytogenes* was cultured from the brain, brainstem, cerebellum, or cervical spinal cord of 8 of the 13 goats submitted for necropsy. Histopathologic lesions were identified in the brainstem of all 13, in the cerebellum of 10, cerebrum of 6, and cervical spinal cord of 2 cases (Figure 2). In the 6 cases involving the cerebrum, the cerebellum, and brainstem were also involved. In all but 3 of the 10 goats with cerebellar involvement, the cerebrum was also affected, and all 10 demonstrated brainstem pathology. Of the 2 cases involving the spinal cord, 1 involved the cerebrum, cerebellum, and brainstem, but the other lacked cerebral involvement (Supplemental Table 1). The histopathological lesions corresponded to the observed antemortem clinical signs in all 13 animals submitted for necropsy. Intracytoplasmic Gram-positive bacilli were identified in 5 of the 13 cases. Concurrent diseases were observed in most necropsied animals and included pulmonary edema and congestion in 5 animals and 2 with GI parasitism. The following concurrent diseases occurred once: colitis, gastroenteritis, contagious ecthyma, previous hepatic laceration, chronic pulmonary nematode endoparasitism, cholangiohepatitis, hepatic lipidosis, cystitis, and dilated cardiomyopathy with hydropericardium.

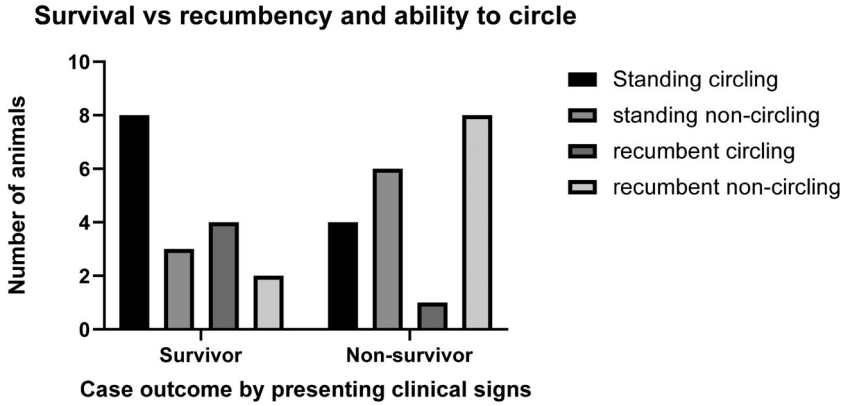

FIGURE 1 Case outcome for animals based on ability or inability to stand and presence or absence of circling at presentation.

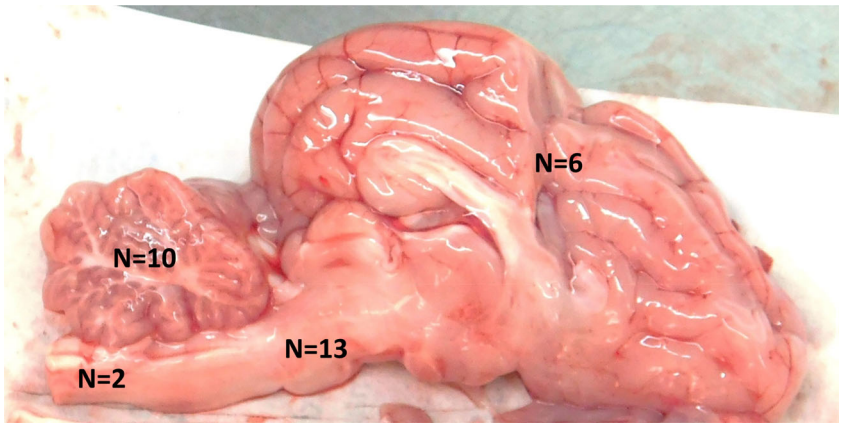

FIGURE 2 Most common locations for lesions in 13 goats that underwent necropsy with encephalitic listeriosis. Photo credit: Dr. Shari Kennedy.

4 | DISCUSSION

In the present study, a detailed evaluation of medical records of goats treated for suspected encephalitic listeriosis from March 2008 through July 2021 at AULATH was performed. The aim was to identify risk factors associated with a greater chance of non-survival to enhance the ability of clinicians to determine the prognosis of animals with encephalitic listeriosis.

The case fatality rate in this study sample was 19/36 (53%). Definitive diagnosis of encephalitic listeriosis was able to be made in 13/36 (36%) of cases based on growth of LM and consistent histological pathology of brain tissue. Presumptive diagnosis was made in the remaining 23/36 (64%) of cases based on classical clinical presentation of encephalitic listeriosis. Published case fatality vary dramatically from 14.3% to 28%[8–10] at the lower end up to 60%-87.5%.[11–13] These vast differences in non-survival rates reported could be because of the difference in true encephalitic listeriosis case fatality rate or neurological case fatality rates. The authors chose to report case fatality rate to better understand the success of treatment of goats presumptively diagnosed with encephalitic listeriosis.

In a previous study, the majority of the animals (40/67) with listeriosis were presented in lateral recumbency.[11] Of the 10 that survived in that study, 9 were still ambulatory at presentation compared to only 1 survivor which presented in lateral recumbency. In contrast, in this study sample 22 of 35 were standing at presentation and of survivors, 11 were standing and 6 were recumbent. While standing or recumbency were not significantly associated with outcome in this study, the greater proportion in lateral recumbency to the previous study might be indicative of more advanced disease in those cases, thus explaining the lower survival rate in that study.[11]

This study demonstrated a statistically significant difference in survival between animals observed to or having a history of circling and those that did not. In this study, 12 of 17 (71%) surviving animals were observed circling or had a history of circling recorded at presentation. This contrasts with 5 out of 19 (26%) non-surviving animals that had a history of or were circling at presentation. Although the ability to stand and circling are not completely independent in a clinical aspect, animals were included with a history of circling to try to understand the interaction of these 2 variables. Of those that were circling at presentation or had history of circling, 12/17 (71%) were standing. Of the 15 animals that were recumbent at presentation, 10/15 (67%) did not have a history of circling before presentation. However, correlation of standing or recumbency versus presence or absence of circling was not statistically significant.

The odds ratio for survival was 6.24 (95% CI: 1.40-23.21) times greater if circling was present. Surviving goats that showed circling at presentation had an average of 5.8 (95% CI: 3.99-7.67) concurrent clinical signs, whereas non-circling non-survivors had an average of 5.7 (95% CI: 4.18-7.35) concurrent clinical signs. Therefore, it does not appear that the non-surviving goats had more severe disease or had more clinical signs than those that survived. Signalment, history other than presence or absence of circling, and treatments administered between groups were similar. A similar finding has not been described by other studies, and it is currently unknown what might explain the apparent protective mechanism of circling observed in this study. It could be argued that animals that were circling were likely still standing as compared to those that were recumbent. Taking animals based on their ability to stand at presentation was not statistically associated with increased likelihood of survival. It is also possible that this might be explained by confounding factors including comorbidities, age, duration of signs at first observation, or delay in treatment that were not recorded in the medical records.

To better understand if there was a correlation between comorbidities and outcome for this study multiple logistic regression was used. Survival was set as the dependent variable and sex, duration of clinical signs, circling, hypersalivation, recumbency, lethargy, anorexia, ataxia, and vestibular, facial, or trigeminal nerve dysfunctions set as the independent variables. No statistical significance of any of the independent variables were found to affect the dependent variable of survival, likely because of the small sample size of the study.

No significant effect on survival was found based on first choice of antimicrobial class within this study. Beta-lactams were chosen as the first class of antimicrobials in 13/36 (36%) of cases, oxytetracycline in 19/36 (53%), and florfenicol in 4/36 (11%) of the cases. Time between first antimicrobial administration and change to another

antimicrobial was relatively uniform for all animals that received more than 1 antimicrobial. On average, goats were maintained on the first antimicrobial for approximately 42 hours before switching to a second antimicrobial class. Reasons for switching were listed as continued deterioration in condition and lack of clinical improvement on the first-choice antimicrobial class. As most of the antimicrobials used during this study have a prolonged duration of action, it is uncertain whether the first-choice antimicrobial was given adequate time to reach treatment effect. Another consideration was if the animals that require more than 1 antimicrobial are more likely to be non-responders to antimicrobials regardless of class selected as first-choice. As the time before switching antimicrobial classes was likely not long enough for treatment effects to be observed, the selection of first-class antimicrobial still might be important but was confounded in the present study.

As in the previously discussed study in which 58/67 (87%) goats presented were females,[11] the authors also observed a high proportion of females, as 26/36 (72%) goats in this study were female. Interestingly, in this study, only 1 out of 10 males survived, with the single surviving male being a buck. Male goats were 14.4 (95% CI: 1.98-166.0) times more likely to be non-survivors than female goats in this study. When wethers were removed from analysis, intact male goats were 9.6 (95% CI: 1.08-115.8) times more likely to be non-survivors than intact female goats. The 9 non-surviving male goats appeared to have similar clinical signs, disease severity, and administered treatment as documented for both the surviving and non-surviving female goats.

It is uncommon to have more than 1 neurologic disease occurring simultaneously within the same animal, it is not unheard of. The concurrent infection with *Parelaphostrongylus* sp. did not exclude the goat with predominantly eosinophilic pleocytosis from analysis in this study as it also was presumptively diagnosed with encephalitic listeriosis. In a previous study, as part of a year-long active surveillance program for transmissible spongiform encephalopathies (TSEs) of small ruminants, brains were collected for histological and immunological testing for TSEs.[4] Neurologic diseases other than TSEs were also identified and evaluated within that study population. Out of 3075 total brains evaluated, 269 lesions were observed, with 21 brains having 2 distinct diagnoses.[4] A goat was diagnosed with concurrent Caprine Arthritis Encephalitis viral infection and a cerebral abscess in a retrospective study of 114 flocks in Greece.[14] These studies demonstrate that concurrent neurologic disease does happen in the natural environments and supports the authors ' decision to include the case of concurrent *Parelaphostrongylus* sp. infection and encephalitic listeriosis in the study.

The observations reported in this study differed from published outcomes of bovine encephalitic listeriosis in several ways. In a previous report describing the clinical findings and treatments of 94 cattle with listeriosis, 25 of 87 treated animals were non-survivors, resulting in a case fatality rate of approximately 29%, which was almost half of that determined in the current study.[15] In that same study, recumbency was described relatively infrequently, with 9 of the 87 treated animals being recumbent on presentation. Only 2 of the recumbent animals survived, and recumbency appeared to be associated with outcome; however, no association statistics were performed.[15] Less severe clinical signs and lower case fatality rates as compared to goats in this study were also described in other reports of bovine listeriosis.[5,16] Lesions were less widespread in the cerebellum, diencephalon, and telencephalon and were described histologically as more chronic in cattle as compared to small ruminants.[5] In cattle, regardless of stage or severity of the disease, the extent of the resulting encephalitis and bacterial load was reported to be significantly less severe than in small ruminants.[16] These reports emphasized the differences in case outcomes and neuropathologic lesions between cattle and small ruminants.

Due to the retrospective nature, 1 of the limitations of this manuscript was the use of medical records to gather case data. Several medical records were missing 1 or more of the study variables; this further reduced an already limited source of information. Manual input or missing diagnosis fields in the medical records limited the ability to search for compatible cases. The medical records software underwent several changes during the study period, increasing the likelihood of case data being lost or inaccurately classified. The current software also contained multiple diagnosis options, including free text input to describe encephalitic listeriosis, and the authors were likely unable to locate all the permutations of encephalitic listeriosis during the case search. The number of cases was another limiting factor to this study, with only 36 presumptively or definitively diagnosed encephalitic listeriosis cases during the study period. This reduced the power of the study and reduces the ability to make strong inferences into prognostic indicators.

In conclusion, in this study sample of goats treated for encephalitic listeriosis, male goats were more likely to die compared to females with similar histories, clinical signs, and treatments. Circling or having a history of circling at presentation was more likely to be associated with survival. Recumbency, presence or absence of head tilt, body temperature at presentation, CSF results, class and number of antimicrobial drugs, and type of anti-inflammatory drugs did not show significant difference in case outcomes. A case fatality rate of 53% was found in this study sample, which is within the wide range of previous reports.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Off-label use of antimicrobials were used at the time of respective treatments because no antimicrobials were/are labeled for treatment of encephalitic listeriosis in goats. However, all antimicrobials utilized in the treatment of animals described in this manuscript followed typical and described doses, routes, and frequencies published and adequate withdrawal times as outlined by FARAD were observed.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed. However, approval was provided by the hospital director of JT Vaughan Large Animal Teaching Hospital of the College of Veterinary Medicine at Auburn University.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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