

# Clinical findings and outcome in goats with discospondylitis and vertebral osteomyelitis

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## Abstract

**Background:** Vertebral infections, including vertebral osteomyelitis, septic phylitis, and discospondylitis, are rarely reported in goats, and when reported, have been largely limited to necropsy case reports.

**Objective:** Describe clinical findings and outcome in goats with vertebral infections evaluated by computed tomography (CT).

**Animals:** Five goats with vertebral osteomyelitis, septic phylitis, and discospondylitis evaluated by CT.

**Methods:** Retrospective case series.

**Results:** The most common presenting complaints were progressive weakness, paresis and recumbency. Three goats were tetraparetic and 2 goats had pelvic limb paraparesis. Clinicopathologic findings included leukocytosis, mature neutrophilia, and hyperfibrinogenemia. The most common vertebrae affected were C7-T1. All 5 goats had discospondylitis with or without vertebral osteomyelitis and septic phylitis. Computed tomographic evidence of spinal cord compression was present in 4/5 goats. Medical management (antimicrobials, physical therapy, analgesia, supportive care) was attempted in 4 goats, and 1 goat was euthanized at the time of diagnosis. All 4 goats that were treated regained ambulatory ability and survived to hospital discharge.

**Conclusions and Clinical Importance:** Despite severity of CT imaging findings, goats with discospondylitis, septic phylitis, and vertebral osteomyelitis can successfully return to ambulatory function. Additional studies are required to determine ideal treatment regimens.

## KEYWORDS

caprine, neuroimaging, neurology, spinal cord disease

## 1 | INTRODUCTION

Vertebral infections, including vertebral osteomyelitis, septic phylitis, and discospondylitis, have been described in a variety of species, including humans, dogs, cats, birds, cattle, pigs, horses,

**Abbreviations:** CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

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goats, and dolphins.<sup>1-9</sup> The most common route of infection is by hematogenous origin from infected sites elsewhere in the body via lymphatic drainage and subsequent arterial spread.<sup>1,2,10</sup> Infection first localizes in the vertebral endplate, likely in slowly flowing venous channels, and then spreads to the adjacent intervertebral disc by diffusion. Finally, the freely communicating venous plexus allows infection to spread to adjacent vertebrae.<sup>2</sup> Other documented sources of infection include trauma, surgery, penetrating wounds, and migrating foreign bodies.<sup>1-3,11</sup> Several bacterial organisms have been identified as causes of vertebral osteomyelitis in other species including *Staphylococcus*, *Streptococcus*, *Pasteurella*, and *Brucella* in dogs; *Rhodococcus* and *Brucella* in horses; and *Pseudomonas* and *Salmonella* in calves.<sup>3-6,12-14</sup> Rare necropsy reports have described *Corynebacterium*- and *Rhodococcus*-associated vertebral osteomyelitis in goats.<sup>7,12</sup>

Vertebral infections have been reported rarely in goats, and when reported, have been limited to necropsy case reports.<sup>7,12</sup> In other species, computed tomography (CT) often is used for antemortem diagnosis of vertebral osteomyelitis, septic phylitis, and discospondylitis.<sup>3</sup> In dogs, treatment approach and duration frequently is guided by progression of radiographic appearance in conjunction with clinicopathologic and physical examination findings.<sup>15</sup> Attempted treatment and clinical outcome of goats with vertebral infections have not been reported previously. Therefore, objective of our retrospective case series was to describe the clinical findings and outcome of goats diagnosed with vertebral osteomyelitis, septic phylitis, and discospondylitis based on CT.

## 2 | MATERIALS AND METHODS

### 2.1 | Case identification

Cases were identified by search of the electronic research and information system (RIS) of all goats that underwent CT at the University of Florida Large Animal Hospital from January 2008 to June 2023, using the search terms “vertebral osteomyelitis” and “discospondylitis.” One additional case also was included that presented to Michigan State University Veterinary Medical Center for which consultation was provided. Cases were included if goats had a diagnosis of vertebral osteomyelitis, discospondylitis, or both based on CT. Cases were diagnosed by board-certified internal medicine specialists and veterinary radiologists.

### 2.2 | Data collection

Electronic medical records were analyzed. The data collected for each goat included: signalment, clinical signs, neurologic examination findings, clinicopathologic results, diagnostic imaging results, treatment, and outcome.

### 2.3 | Diagnostic imaging

Data on the CT features of vertebral osteomyelitis and discospondylitis were extracted from finalized radiology reports. All imaging was reviewed for accuracy by a veterinary radiologist (EH). Characteristic CT features of vertebral osteomyelitis included multifocal bone lysis with thinning or complete disruption of the cortical margins, sclerosis, irregular periosteal reaction and formation of sequestra. The CT features of discospondylitis included lysis of the vertebral endplate and periosteal proliferation adjacent to the intervertebral disc spaces.<sup>3</sup> Computed tomographic features of septic phylitis included reactive bony involvement and osteolysis centered on the vertebral physis, without initial involvement of the disc space.<sup>16</sup> When radiographs or magnetic resonance imaging (MRI) also were performed, data also were extracted from finalized radiology reports. Magnetic resonance imaging was advantageous for the assessment of epidural empyema and abscessation, which have been reported to occur with vertebral infections.

When multiple imaging modalities were used, the reports of each imaging modality were recorded separately. Three patients had multiple CTs performed: 1 of these also had MRI in addition to multiple CTs, and another goat also had radiographs performed in addition to multiple CTs.

### 2.4 | Treatment and outcome

Treatment protocols were recorded for each patient including antimicrobial type, dose, frequency, and duration of treatment. Outcome was recorded based on survival to hospital discharge and follow-up for all cases. Euthanasia and necropsy findings were recorded when applicable.

### 2.5 | Statistical analysis

Descriptive statistics were used to report imaging and clinical findings. Numerical values are reported as median and range unless otherwise specified.

## 3 | RESULTS

### 3.1 | Patient signalment

Five goats met the inclusion criteria. Breeds included Boer (2), La Mancha (1), Nigerian Dwarf (1), and Tennessee Fainting Goat (1). There were 4 males (2 intact, 2 castrated) and 1 female. Median age at admission was 6 weeks (range, 3-78 weeks). Median weight was 5.8 kg (range, 2.6-36 kg). Intended use was as companion animals (4) and breeding animal (1). Clinical findings are reported in Supplemental Table 1.

### 3.2 | Presenting complaint/historical findings

The most common presenting complaints included progressive weakness, paresis and recumbency. Three goats were tetraparetic and 2 goats had pelvic limb paraparesis. At admission, 4 goats were not able to stand or ambulate on their own. One goat initially was reported to be recumbent in the field. This goat had been receiving antimicrobial treatment before admission and was able to walk but was weak and markedly ataxic in all 4 limbs. Three goats had a history of failure of transfer of passive immunity and failure to thrive as neonates. None had a reported history of trauma.

### 3.3 | Clinical findings

Physical examination findings were largely unremarkable with the exception of neurologic locomotor deficits. Neurologic evaluation identified normal mentation and normal cranial nerve examination in all goats (Supplemental Table 2). Neurolocalization was determined to be spinal in all cases. All 3 tetraparetic goats were neurolocalized to the cervical spinal cord and the paraparetic goats were neurolocalized to the thoracolumbar spinal cord.

### 3.4 | Clinicopathologic findings

Clinicopathologic findings were variable and included leukocytosis (3/5 goats), mature neutrophilia (3/5 goats), and hyperfibrinogenemia (2/4 goats; Supplemental Table 1). Blood cultures were performed on 2 goats that had not previously been started on antimicrobial therapy before admission. One goat had growth of *Streptococcus bovis* on blood culture. The remaining blood culture was negative.

One goat (Goat 1) had lumbosacral cerebrospinal fluid (CSF) centesis performed that yielded normal CSF findings (white blood cell count, 2/ $\mu$ L; reference range, 0-5/ $\mu$ L; red blood cell count, 10,150/ $\mu$ L; reference range, 0-2/ $\mu$ L; total protein concentration could not be obtained because of insufficient volume; reference range, 8-70 mg/dL; no cytologic abnormalities were detected).

### 3.5 | Diagnostic imaging findings

One goat had 4 CTs (Goat 3) and 1 goat had 3 CTs and 1 MRI (Goat 4) performed. One goat had 2 CTs and radiographs (Goat 2), and the remaining 2 goats had 1 CT performed (Goats 1 and 5). Aggressive vertebral lesions, as characterized by the presence of osteolysis, sclerosis and irregular osteoproliferation, were identified in all goats (Figure 1A-E). The most common vertebrae affected were C7 and T1, in 3/3 tetraparetic goats. Polyostotic lesions were identified in all goats. All goats had lysis of opposing endplates with or without narrowing of the intervertebral disc space to support a diagnosis of discospondylitis (Figure 1A-E). Three goats had compressive vertebral fractures. Two of these 3 goats had fractures centered on C7

(Figure 1C,D, Goats 3 and 4), whereas the remaining goat had a fracture centered on T4 (Figure 1E, Goat 5). These fractures were associated with severe lysis and foreshortening of the affected vertebra. These goats also had severe narrowing of the adjacent intervertebral disc spaces with lysis of the vertebral endplates. Three goats had secondary moderate to severe extradural spinal cord compression associated with the presence of severe soft tissue swelling. This finding was predominantly left-sided in Goat 4 and observed on both CT and MRI (Supplemental Figure 1). Goat 5 had ventral soft tissue swelling and moderate kyphosis resulting in a severe compressive myelopathy (Figure 1E).

Radiography in Goat 2 identified aggressive polyostotic lesions of C3-C4 and C7-T1, which were confirmed on CT (Supplemental Figure 2, Goat 2). Goat 1, with paraparesis, had lysis of the T12 vertebra primarily centered on the physal region combined with an expansile, aggressive, fluid attenuating mass centered on T12-T13 with associated severe spinal cord compression (Supplemental Figure 3, Goat 1).

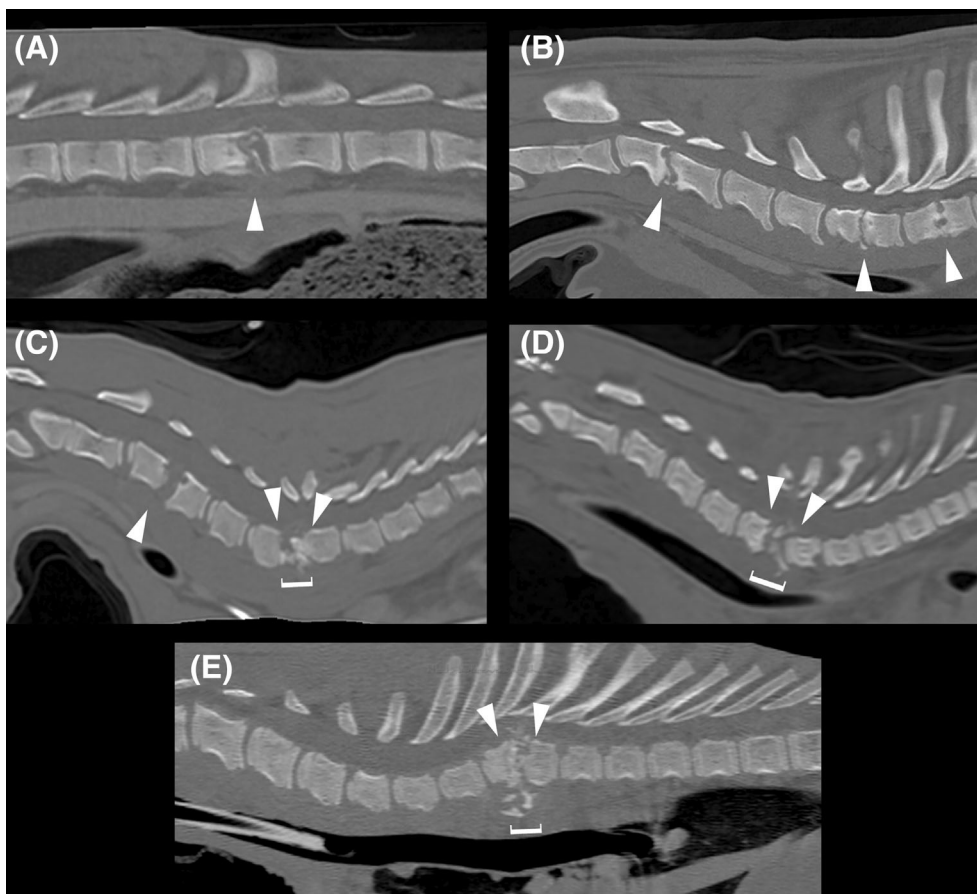
Goat 4 also had lysis of the left humeral proximal physis and metaphysis. Goat 5 had moderate enlargement and fluid cavitation of the left superficial cervical lymph node with a thick peripheral contrast-enhancing rim, compatible with an abscess. A similar lesion, also likely representing an abscess, was present in the left epaxial and scapular musculature region.

Repeat CT was available in 3/5 (60%) cases and was used in conjunction with physical examination and clinicopathologic findings to guide duration of treatment (Figure 2). All goats with repeated CT imaging had evidence of progressive remodeling of osseous lesions with resolution of the extradural soft tissue spinal cord compression, as demonstrated in 1 of the goats with a pathologic C7 compression fracture (Supplemental Figure 4, Goat 3).

### 3.6 | Treatment

Medical management was pursued in 4 goats, whereas 1 goat was euthanized at the time of diagnosis. Treatment consisted of long-term antimicrobials, physical therapy, anti-inflammatory medications, analgesia, and supportive care. The anti-inflammatory medication of choice in all cases was flunixin meglumine and the analgesic medicine of choice was gabapentin. Antimicrobials included oxytetracycline, penicillin, gentamicin, florfenicol, ceftiofur sodium, ceftiofur crystalline free acid, and tulathromycin.

Goat 2 was treated with ceftiofur sodium (2.2 mg/kg IM q12h) for 8 weeks in combination with gentamicin (5 mg/kg IM q24h) for weeks 1-2 and procaine penicillin (22 000 IU/kg IM q12h) for weeks 3-4, and then was lost to follow-up until a follow-up phone call 2 years later. Goat 3 received antimicrobials for 6 months total: potassium penicillin (22 000 IU/kg IV q6h) and oxytetracycline (5 mg/kg IV q12h) for 3 weeks, followed by florfenicol (40 mg/kg SC q48h) for 12 weeks, and tulathromycin (2.5 mg/kg SC q168h) for another 10 weeks. Goat 4 received antimicrobials for 8 months total: potassium penicillin (22 000 IU/kg IV q6h) and ceftiofur sodium (5 mg/kg



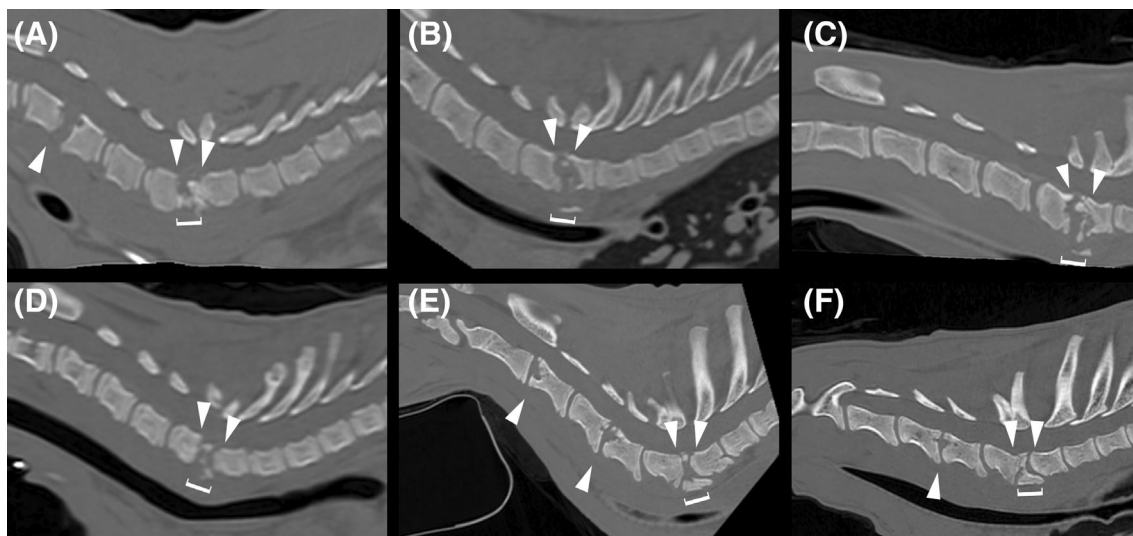
**FIGURE 1** Sagittal computed tomographic images in a bone algorithm of 5 goats with vertebral infection. (A) Severe osteolysis centered on the caudal physal region of T12 (arrowhead), supporting a diagnosis of septic physisitis, with mild lysis of the caudal endplate, as well as the T13 cranial endplate, indicative of concurrent discospondylitis. Centered on this region, there was a large fluid-cavitated mass, likely representing an abscess associated with severe spinal cord compression (Goat 1). (B) Severe multifocal osteolysis of the opposite endplates of C3-C4, C7-T1 and T2-T3 in Goat 2 with intervertebral disc narrowing (arrowheads). (C) Near complete lysis and collapse (compression fracture) of C7 (bracket) with lysis of the opposing C6 and T1 vertebral endplates (arrowheads), as well as C3-C4, indicative of discospondylitis (Goat 3). (D) Near complete lysis and collapse (compression fracture) of C7 (bracket) with lysis of the opposing C6 and T1 vertebral endplates (arrowheads), indicative of discospondylitis (Goat 4). (E) Near complete lysis and collapse (compression fracture) of T4 (bracket) with severe lysis of the caudal T3 and cranial T5 endplates (arrowheads) compatible with discospondylitis (Goat 5). Moderate kyphosis with peripheral distribution of multifocal mineralization at the fracture site is associated with moderate to severe narrowing of the vertebral canal.

IV q12h) for 4 weeks, florfenicol (40 mg/kg SC q48h) for the next 6 weeks, and tulathromycin (2.5 mg/kg SC q168h) for another 22 weeks. Goat 5 remained on antimicrobials (3 months at the time of writing): ceftiofur crystalline free acid (6.6 mg/kg IM once) with procaine penicillin (22 000 IU/kg IM q12h) for 1 week, then florfenicol (40 mg/kg SC q48h) for 4 weeks, and remains on tulathromycin (2.5 mg/kg SC q168h, 7 weeks at the time of writing). Without antemortem culture results to guide antimicrobial choice in the majority of cases, antimicrobial choice was clinician-dependent and based on broad spectrum antimicrobial activity and long-acting duration of action. Duration of treatment was guided by clinical progression and imaging findings (ie, static appearance of lesions on CT) and extrapolated from treatment recommendations used in dogs. No adverse effects associated with antimicrobial administration were noted in any goat. Food Animal Residue

Avoidance Databank (FARAD) requests for recommended withdrawal intervals were submitted for all medications administered in an extra-label manner.

Physical therapy was utilized in the treatment of 3 goats, including passive range of motion exercises, mobility devices, and electroacupuncture. Two of the tetraparetic goats were in carts for a period of time before regaining the ability to walk unassisted.

During treatment, 3 goats were diagnosed with concurrent disorders. In addition to the vertebral osteomyelitis and discospondylitis, 3 were diagnosed with pneumonia based on clinical signs and imaging findings (Goats 3-5), and 1 of these also had concurrent left humeral physisitis (Goat 4). Complete resolution of the pneumonia was achieved within 3-6 weeks of diagnosis as confirmed by resolution of clinical signs and follow-up CT (2 goats) and resolution of clinical signs only (1 goat).



**FIGURE 2** Sagittal CT images of Goat 3 (A-C) and Goat 4 (D-F) reformatted using a bone algorithm. Goat 3 had near complete lysis and collapse (compression fracture, bracket) of C7 with concurrent C3-C4 and C6-T1 discospondylitis (arrowheads; A, at admission). On repeat CT, progressive remodeling of the C7 vertebra and affected intervertebral disc spaces is observed with developing spondylosis deformans at C6-T1 (B, 5 weeks after initial admission; C, 14 weeks after initial admission). Goat 4 also had complete lysis and collapse (compression fracture, bracket) with concurrent C2-C3, C4-C5 and C6-T1 discospondylitis (arrowheads) most advanced on the second repeat CT (D, at admission; E, 17 weeks after initial admission; F, 29 weeks after admission). On the later CT study, remodeling of the C7 vertebra and affected intervertebral disc spaces is observed.

### 3.7 | Outcome

At time of discontinuation of treatment, no ataxia or proprioceptive deficits were detected when observing ambulation in 2 goats (Goats 3 and 4), although complete neurologic examinations were precluded by patient demeanor. A third goat (Goat 2) was reported by the owner to have persistent mild left forelimb lameness that reportedly did not negatively impact the animal's quality of life.

Four goats survived to hospital discharge, and 1 was euthanized after diagnosis without treatment (Goat 1). Goats 5, 3, and 4 remain alive and ambulatory at 3 months, 7 months and 20 months after initial presentation (at time of writing). These 3 goats were companion animals and returned to their intended use. One goat (Goat 2), intended to be used as a breeding animal, survived for 2 years but ultimately was euthanized 2 years after hospitalization because of aggressive buck behavior.

The nonsurviving goat underwent necropsy, which identified severe, pyogranulomatous vertebral osteomyelitis of the T12-T13 region, confirming the clinical diagnosis of a vertebral abscess. Marked axonal degeneration secondary to compression of the spinal cord by the abscess was present. Anaerobic culture of the abscess yielded heavy growth of *Fusobacterium* spp.

## 4 | DISCUSSION

We report the clinical features, imaging findings, treatment, and outcome of 5 goats diagnosed with discospondylitis and vertebral osteomyelitis, with successful treatment in 4 of these goats. This

retrospective case series provides evidence that vertebral infections in valuable, young goats potentially can be successfully treated with prolonged medical management, with potential return to ambulation. Despite the apparent severity of lesions on imaging, 4 goats returned to ambulation after paraparesis or tetraparesis. All goats were admitted with a similar clinical history of progressive paresis and, ultimately, recumbency. However, determination of causality and inference of an ideal treatment approach cannot be made because of the small sample size.

Three of the 5 goats had a history of failure of transfer of passive immunity, suggesting that neonatal sepsis might play an important role in the development of vertebral osteomyelitis and discospondylitis. Additionally, the 3 youngest goats all had evidence of pneumonia during treatment, which also might support the hypothesis of neonatal sepsis playing a role in the pathophysiology. Vertebral osteomyelitis, septic physisitis, and discospondylitis most often originate from hematogenous spread of bacteria from a septic source, thereby supporting a potential link with neonatal sepsis.<sup>2,10</sup> Such pathophysiology also is supported by the presence of septic physisitis in the left humerus of 1 goat. Based on the distribution of lesions, sites that are more metabolically active might be the primary sites of infection (growth plates, intervertebral discs). Radiographically, differences exist among vertebral osteomyelitis, septic physisitis, and discospondylitis. However, increased disease severity often will cause these infections to occur concurrently, making it more difficult to determine the primary site of infection. A previous study of 30 dogs proposed that making a radiographic distinction between vertebral physisitis and discospondylitis might hold clinical merit in younger dogs.<sup>16</sup> In that study, physisitis lesions tended to induce collapse of the vertebral body and



subsequent kyphosis, whereas discospondylitis lesions tended to cause shortening of the affected vertebral bodies but less commonly caused angular deformities of the spine. Given the limited number of animals and severity of lesions in the goats of our study, this differentiation was difficult to make, but could warrant further investigation for its clinical implications.

Although few studies describe vertebral infections in goats, studies have been published regarding the clinical presentation, diagnosis, and outcome of vertebral infections in cattle and dogs. In a study of 14 calves, clinical signs of cervico-thoracic vertebral osteomyelitis began at 2 to 9 weeks of age.<sup>4</sup> All 14 calves in that study had lesions affecting C6-T1. The C7 and T1 vertebrae were affected in 3/5 goats in our study, suggesting a predilection in ruminants for vertebral osteomyelitis affecting the cervico-thoracic junction. The exact mechanism for this apparent predilection has not been found, but it theoretically could be related to hematogenous spread through the communication between the intracavity venous system and the vertebral venous system, as well as the presence of the ventral external vertebral plexus at the level of the cranial thoracic and cervical regions.<sup>4,10</sup> Clinicopathological findings were variable, but included a leukocytosis characterized by mature neutrophilia as well as hyperfibrinogenemia, similar to what has been reported previously in calves with vertebral osteomyelitis.<sup>4</sup> Although only 1 goat in our study had CSF analysis performed, no abnormalities were found in 10 of 14 calves for which CSF analysis was available in a prior study.<sup>4</sup> It is not surprising that CSF analysis was normal, because the primary lesion in these cases likely was extradural. Interestingly, only 1 goat was febrile on admission, suggesting that lack of fever should not rule out an infectious cause.

In a recent multicenter study investigating dogs with discospondylitis, 27% (38/143) had positive blood cultures.<sup>3</sup> This blood culture positivity was slightly lower than previously reported.<sup>3</sup> In previous studies in dogs, *Staphylococcus* species were the most commonly isolated bacteria on blood culture.<sup>3,17,18</sup> Other commonly isolated bacteria include *Streptococcus* and *Pasteurella* species.<sup>3</sup> In ruminants, osteomyelitis has been shown to develop secondary to traumatic wounds, and *Actinomyces* has been reported as a causative organism.<sup>7</sup> One goat in our study had a blood culture positive for *Streptococcus bovis* and another goat had growth of *Fusobacterium* sp. on necropsy culture of a vertebral abscess. Rare case reports have described *Corynebacterium* and *Rhodococcus* sp. as causative agents of osteomyelitis in goats.<sup>7,12</sup>

Follow-up advanced imaging is ideal but not feasible in all cases. In our cases, follow-up CTs were performed in 3 treated goats to help guide duration of antimicrobial treatment. Clinical improvement in our patients was seen far sooner than radiographic improvement, with clinical improvement being noticed in the first 1-2 weeks. A retrospective study following the radiographic findings of dogs recovering from discospondylitis had findings similar to those in our case series. Clinical signs in the dogs were reported to have improved within the first 10 days of antibiotic treatment, but radiographic deterioration continued before regression and signs of radiographic recovery were observed.<sup>15</sup> This observation emphasizes the importance of

recognition that osseous imaging findings might be misleading during the healing process. The extent and progression of osseous spinal changes do not always correlate well with clinical signs, indicating the continued need for long-term antimicrobials even when the patient is clinically improving. Clinical improvement often results from regression of soft tissue swelling and decreased spinal cord impingement. Repeat advanced imaging (CT, MRI) could be helpful to assess soft tissue components of the lesions and detect regions of active inflammation. Although MRI would be the preferred modality for soft tissue imaging, soft tissue changes were noted to be improved on repeat CT in the goats of our study. This finding also emphasizes the importance of performing CT angiography to better identify soft tissue lesions. Although we were able to repeat advanced imaging, repeat radiographs could be taken in the field for goats that cannot receive hospital care, but the challenge of identifying soft tissue improvement would remain. Although most dogs with osteomyelitis or discospondylitis receive medical treatment alone, surgical approaches are described and include laminectomy or discectomy.<sup>3,17</sup> Surgical options were not pursued in any of our goats, and thus it cannot be determined if surgical intervention would have improved outcome or shortened the treatment period.

In other species, antimicrobial treatment is recommended for several months to treat osteomyelitis and discospondylitis. In a retrospective study of dogs with discospondylitis, mean duration of treatment was 53.7 weeks.<sup>17</sup> The appropriate duration of antimicrobial treatment in goats is unknown. Therefore, treatment in this case series was guided by the recommendations used in dogs. However, this approach resulted in prolonged antimicrobial use and a number of antimicrobials were used in an extra-label manner in the goats reported here. With the exception of ceftiofur sodium, none of the antimicrobials used in the goats in our study are labeled for use in goats, and ceftiofur sodium is labeled for treatment of respiratory disease. However, many antimicrobials can be used in goats, a minor species, legally in an extra-label manner under a valid veterinary-client-patient relationship and under the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994. Regardless, veterinarians should adhere to extra-label use guidelines, especially given the status of goats as both production animals and companion animals and the lengthy treatment duration seemingly required for treatment of vertebral infections.

Our case series was limited by its retrospective nature, small sample size, and nonstandardized diagnostic and therapeutic approaches. Despite these limitations, we demonstrated possible return to ambulation in goats diagnosed with vertebral infections (vertebral osteomyelitis and discospondylitis). Over the course of treatment, goats regained mobility and progressed from full tetra- or paraparesis to regaining the ability to walk in a matter of months. Our study lacks the power to establish a causal effect of the treatments administered on outcome, but the knowledge that treatment can be considered in high-value goats that otherwise might be euthanized because of the severity of lesions on diagnostic imaging is of clinical relevance. Additional studies are required to determine the ideal treatment approach for such cases.

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**CONFLICT OF INTEREST DECLARATION**

Authors declare no conflict of interest.

**OFF-LABEL ANTIMICROBIAL DECLARATION**

The goats described in this case series received a variety of antimicrobials (penicillin, oxytetracycline, florfenicol, ceftiofur, gentamicin, tula-thromycin) administered in an extra-label manner as described within the manuscript.

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

Authors declare no IACUC or other approval was needed.

**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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