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Clinical presentation, medical management, and outcomes in 35 hospitalized sheep diagnosed with bluetongue virus disease

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Abstract

Background: There is only limited information on the clinical presentation, medical management, and outcomes of hospitalized sheep diagnosed with bluetongue virus (BTV) disease.

Objectives: To describe the signalment, history, clinical signs, clinicopathological findings, medical management, and clinical outcomes of sheep diagnosed with BTV disease.

Animals: Thirty-five hospitalized sheep with BTV disease.

Methods: Retrospective case series. Medical records from 1989 to 2021 were evaluated. History, signalment, clinical signs, laboratory test results, treatments, and outcomes were recorded.

Results: BTV disease was diagnosed from July to December, with a peak proportion (43%; 15/35) of diagnoses recorded in October. Pyrexia and anorexia, respiratory disease, vasculitis, coronitis and lameness, and ulcerative mucosal lesions were present in 71%, 71%, 66%, 49%, and 22% of sheep, respectively. BTV serotypes 10, 11, 13, and 17 were identified, with serotype 17 (75%) being the most frequent. Management of cases included administration of antimicrobials (89%), anti-inflammatories (77%), IV fluids (60%), vitamins (20%), proton-pump inhibitors (14%), diuretics (9%), and antioxidants (9%). Six ewes were pregnant on presentation, but none aborted. Six (17%) sheep died or were euthanized because of clinical deterioration, whereas 83% were discharged.

Conclusions and Clinical Importance: The proportion of sheep that survived BTV disease after treatment was relatively high. Serotyping of BTV is recommended because of the mismatch between frequently identified serotypes and the serotype present in the vaccine.

KEYWORDS

coronitis, ovine, serotype, ulcers, vaccine, vasculitis

Abbreviations: BTV, blue tongue virus; CBC, complete blood count.

1 | INTRODUCTION

Bluetongue virus (BTV) disease is an arthropod-borne orbivirus disease affecting sheep, goats, and cattle. Midges of the genus *Culicoides* are the vectors transmitting BTV between hosts.[1] However, BTV can also be transmitted directly by contact,[2] mechanically by ticks and hypodermic needles,[3,4] venereally,[5] and vertically.[6] Bluetongue is a disease of mandatory notification to the World Organization of Animal Health. BTV occurs on all continents except Antarctica.[7] In the United States, BTV disease was reported in Arizona, California, Florida, Georgia, Idaho, Kansas, Louisiana, Maryland, Mississippi, Missouri, Montana, Nebraska, Nevada, New Mexico, Oklahoma, Oregon, South Carolina, South Dakota, Texas, and Washington.[8] At least 28 distinct serotypes of BTV were described, and multiple putative serotypes have been identified in addition since 2014.[9-11] Disease severity depends on the strain of BTV, with sheep being the most susceptible ruminant species.[12,13] European fine wool and mutton sheep are more susceptible to BTV infections than indigenous breeds,[14] and Hartline/Suffolk crossbred sheep are more susceptible than purebred Hartline sheep.[15] Clinical signs of BTV disease include pyrexia, nasal discharge, congestion of nasal, oral, and ocular mucosa, facial edema, severe mucosal erosions, respiratory distress, coronitis and lameness, cyanosis of the tongue (blue tongue), abortion, and death.[12,13] Costs associated with BTV disease include treatment, death, abortions, decreased weight gain, control measures, and trade restrictions.[16] Research efforts focus on BTV surveillance programs and vaccination strategies.[17] In the United States, the recommended commercially available vaccine in sheep contains serotype 10[18]; however, cross-protection among serotypes is rare.[19]

Although clinicopathological findings associated with specific strains of BTV in outbreak scenarios or after experimental infection were described in earlier studies,[20-25] limited information is available describing presentation, management, and outcomes of hospitalized sheep diagnosed with BTV disease. Therefore, there is a knowledge gap regarding individual animal care and prognosis in sheep for which intensive treatment is necessary. We hypothesized that the overall prognosis for survival of BTV in hospitalized sheep is favorable. Although specific information about the infective serotype is essential for surveillance and the development of vaccines, clinical management of affected animals precedes the identification of the causative serotype. Based on our clinical experience, we hypothesized that the BTV strain type most frequently diagnosed in sheep might not be included in the only commercially available vaccine. Our objectives were to (1) describe the signalment, history, clinical signs, and clinicopathological findings of hospitalized sheep with BTV disease, (2) describe the medical management and outcomes of sheep diagnosed with BTV disease, and (3) identify the most frequent BTV strains leading to clinical disease in hospitalized sheep.

2 | MATERIALS AND METHODS

2.1 | Animals

Medical records of sheep diagnosed with BTV disease were evaluated at the William Pritchard Veterinary Medical Teaching Hospital, University of California Davis, from 1989 to 2021. History, signalment, clinical signs on presentation, laboratory test results (CBC and serum biochemical analysis), treatments, and clinical outcomes were recorded. The history recorded included the month BTV disease was diagnosed, recent travel, and vaccination status against BTV. Signalment included breed, sex, age, weight, use (production or companion), and pregnancy status. Outcomes were categorized as alive (discharged from the hospital) and dead (natural death or euthanized). For pregnant animals, abortion or live lambs born were recorded. The BTV serotype was recorded when available. Identification of BTV was performed at the California Animal Health and Food Safety Laboratory in Davis, California, and serotyping was performed at the National Veterinary Laboratory Services in Ames, Iowa.

2.2 | Statistical analysis

Proportions for the month when BTV disease was diagnosed, recent travel, vaccination status against BTV, breed, sex, age, weight, use, and pregnancy status were calculated. Clinical signs on examination were categorized as nonbody system specific signs (pyrexia, anorexia), vasculitis (edema, congestion of nasal and oral mucosa, and cyanosis of the tongue), ulcerative mucosal lesions, coronitis and lameness, and respiratory disease. Serum biochemical analysis and CBC findings were summarized. Specific tests for detecting BTV were recorded. Medical treatments were categorized as antimicrobials, anti-inflammatories, IV fluid administration, proton-pump inhibitors, diuretics, vitamins, and antioxidants. Duration of hospitalization, abortion rate, death rate, and frequency of BTV serotypes were calculated. Data were analyzed using statistical software (GraphPad Prism v9.4.0, LaJolla, California).

3 | RESULTS

3.1 | History findings

Thirty-five sheep were hospitalized for BTV disease. Fifteen (43%), 8 (23%), 5 (14%), 4 (11%), 2 (6%), and 1 (3%) sheep were diagnosed in October, September, August, November, July, and December, respectively. A total of 0 to 4 cases per year were diagnosed from 1989 to 2020, whereas 12 cases were diagnosed in 2021. None of the sheep were vaccinated against BTV. Seven sheep (20%) were purchased recently (within 2 weeks) and transported or participated in a livestock show. Twelve (34%), 6 (17%), 3 (8%), 3 (8%), 2 (6%), 2 (6%), and 2 (6%) were Dorper, Suffolk, Dorset, Rambouillet, Hampshire, Jacob, and mixed breed, respectively. Mini-Southdown, Finnish, Painted Desert Sheep, Katahdin, and Southdown breeds were each represented by 1 sheep (3%). Twenty-two (63%) sheep were female, whereas 13 (37%) were male (5 wethers and 8 rams). The median (range) weight for all sheep was 80 kg (30-135.4 kg), and the median age was 2 years (6 months to 8 years). Twenty-two sheep (63%) were production animals (including show animals), whereas 13 (37%) were pets. Six ewes were pregnant at the time of hospitalization.

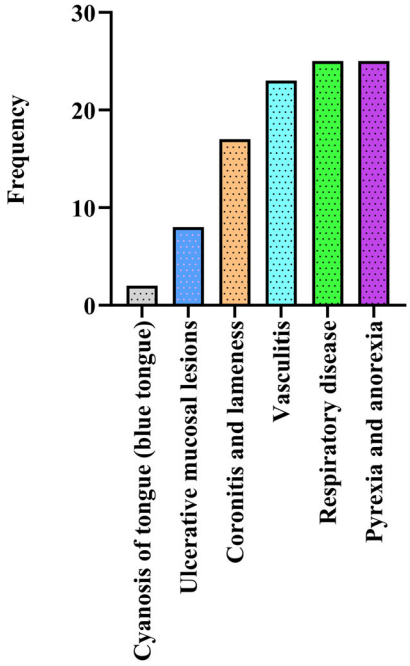

FIGURE 1 Frequency of clinical examination findings in 35 hospitalized sheep diagnosed with bluetongue virus disease.

3.2 | Clinical examination findings

Twenty-five (71%), 25 (71%), 23 (66%), 17 (49%), and 8 (22%) sheep had pyrexia and anorexia, respiratory disease, vasculitis, coronitis and lameness, and ulcerative mucosal lesions, respectively. Only 2 sheep (6%) developed cyanosis of the tongue. The median (range) rectal temperature for sheep that developed pyrexia was 40.9°C (39.8°C-41.7°C). Respiratory disease signs included bilateral mucoid or serous nasal discharge (n = 17, 49%), harsh bronchovesicular sounds (n = 11, 31%), tachypnea (n = 6, 17%), coughing (n = 3, 9%), wheezing or crackling sounds on auscultation (n = 2, 6%), and open mouth breathing (with secondary hypersalivation; n = 2, 6%). Vasculitis included edema of the face (lips, tongue, muzzle, ears, conjunctiva, and mandible; n = 20, 57%), distal limbs and coronary band (n = 6, 17%), neck and brisket (n = 4, 11%), ventral abdomen (n = 3, 9%), udder (n = 1, 3%), tail base (n = 1, 3%), and vulva (n = 1, 3%). The clinical examination findings are summarized in Figure 1. Coronitis was identified by hyperemia and edema extending from the coronary band to the carpal and tarsal joint, with lameness observed in 2 or more limbs. Ulcerative mucosal lesions were present on nares (n = 3, 9%), lips (n = 2, 6%), tongue (n = 2, 6%), hard palate (n = 2, 6%), buccal mucosa (n = 1, 3%), and gingiva (n = 1, 3%).

3.3 | CBC, serum biochemical analysis, and BTV testing

A CBC was performed in 19 sheep. Leukopenia characterized by lymphopenia was identified in 13 sheep (68%), whereas leukopenia characterized by neutropenia with a left shift was identified in 8 sheep (23%). Thrombocytopenia, anemia, and hyperfibrinogenemia were identified in 10 (53%), 2 (11%), and 2 (11%) sheep, respectively. The results of the CBC analysis are summarized in Figure 2.

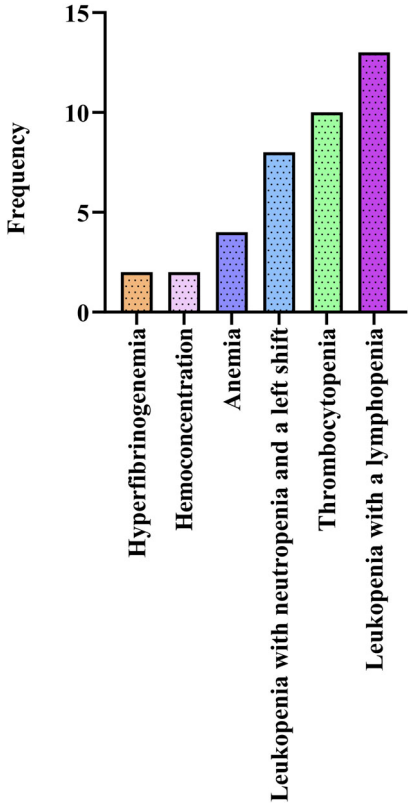

FIGURE 2 Frequency of CBC findings in 35 hospitalized sheep diagnosed with bluetongue virus disease.

Serum biochemical analysis of venous blood samples was performed in 27 sheep. Hypoproteinemia characterized by hypoalbuminemia, hypokalemia, and hyperchloremia and hyperlactatemia were identified in 21 sheep (78%), 15 sheep (56%), 11 sheep (41%), respectively. The evaluation of acid-base abnormalities associated with the respiratory system was inconsistent because venous blood samples were evaluated. Increased creatine kinase activity was identified in 5 sheep (19%). Further diagnostic tests, including radiographic and ultrasonographic examination, were performed to evaluate other causes of respiratory disease, hypersalivation, and lameness in 10 sheep (29%).

Detection of BTV was performed by real-time PCR and virus isolation in 29 and 2 samples, respectively. Agar gel immunodiffusion and antigen-capture ELISA were performed to detect BTV on 2 and 1 sample, respectively. Complement fixation test was performed on the lungs and spleen in a single sample. The BTV serotype was identified in samples from 20 sheep. Fifteen (75%), 2 (10%), 2 (10%), and 1 (5%) samples were serotypes 17, 13, 10, and 11, respectively.

3.4 | Hospitalization, medical treatments, and clinical outcomes

Thirty-one sheep (89%), 27 (77%), 21 (60%), 7 (20%), 5 (14%), 3 (9%), 3 (9%), and 2 (6%) were administered antimicrobials, anti-inflammatories,

IV fluids, vitamins, proton-pump inhibitors, diuretics, antioxidants, and intranasal oxygen, respectively. Classes of antimicrobials administered included macrolides (tulathromycin; n = 18, 51%), beta-lactams (procaine penicillin G, ceftiofur, ampicillin; n = 7, 20%), and amphenicols (florfenicol; n = 3, 9%). Anti-inflammatories administered included flunixin meglumine (IV; n = 26, 74%) and meloxicam (PO; n = 5, 14%). Crystalloids fluids administered included IV sodium chloride (0.9% sodium chloride, Baxter, Deerfield, IL), lactated Ringers (Vetivex, Dechra, Overland Park, Kansas), and Plasma-Lyte (Plasma-Lyte A 148, Baxter, Deerfield, Illinois) with or without additives, such as potassium chloride, dextrose, and vitamins. Vitamins administered parenterally included thiamine (n = 5, 14%) or multivitamin B combinations (n = 2, 6%). Proton-pump inhibitors, diuretics, and antioxidants administered included pantoprazole (n = 5, 14%), furosemide (n = 3, 9%), and selenium (n = 3, 9%), respectively.

The median (range) time for hospitalization was 5 (1-25) days. None of the 6 pregnant ewes aborted and delivered live, thriving lambs on follow-up (12 weeks, preweaning period) with the owners. Of the 35 sheep, 83% were discharged from the hospital, whereas 6 sheep (17%) did not survive (4 were euthanized because of clinical deterioration and 2 died). Of the nonsurvivors, 4 sheep were female, and 2 were males. Three nonsurvivors were diagnosed with BTV serotype 17, and 1 nonsurvivor was diagnosed with BTV serotype 10, whereas the BTV serotype was not identified for 2 nonsurvivors. Necropsy findings included whole-body edema, bronchointerstitial pneumonia, and petechial hemorrhages on serosal surfaces of the thorax.

4 | DISCUSSION

The proportion of sheep that survived BTV disease and was discharged from the hospital after treatment was relatively high. This suggests that sheep diagnosed with BTV disease undergoing supportive treatment have a good prognosis for survival. Anecdotally, BTV disease is reported in the late summer and early fall months, with cases peaking in August and October in California. The diagnosis of BTV disease in July and December might indicate a change in the activity of the *Culicoides*. This finding is essential for including BTV disease as a differential diagnosis from July to December when signs consistent with BTV disease are present. Transportation of sheep after purchase or participating in livestock shows might increase the likelihood of exposure to infected vectors.[26] The overrepresentation of BTV cases in 2021 could be related to weather, vector activity, or more accessible BTV molecular testing methods.

Despite the Dorper comprising a small cohort (<10%) of sheep breeds we examine in our clinic practice, the breed was overrepresented in our study, in contrast to lower susceptibility in African breeds (such as Dorper) reported earlier.[27] Other studies report a higher susceptibility to BTV and associated severe clinical signs in Dorset sheep, whereas only 8% of cases in our study were Dorset.[28,29] The differences and similarities between our study and previous studies might be attributed to different BTV strains involved, management, and other environmental, or host factors. A higher proportion of sheep in our study were raised for production than pets. Sheep raised for production purposes are more likely to be large flocks and travel to and from sale barns or livestock shows, and therefore, transmission of the BTV might be efficient. Furthermore, the negative economic impact on production flocks will motivate owners to seek veterinary care.

BTV has a high affinity for erythrocytes,[30] but its target cells are endothelial cells,[31] resulting in endothelial damage, vasculitis, edema, and hemorrhage. Pyrexia and anorexia are considered early clinical signs of BTV disease, whereas respiratory distress and esophageal paralysis are considered severe forms of BTV disease.[13] In our study, 71% of sheep exhibited respiratory disease signs, which prompted owners to seek veterinary care. The esophageal paralysis or oral ulcerations might explain the hypersalivation observed in some sheep. Despite the disease's descriptive name, only 2 sheep demonstrated cyanosis of the tongue in our study.

Leukopenia characterized by lymphopenia is consistent with a viral infection. Leukopenia characterized by neutropenia with a left shift suggests severe inflammation. Thrombocytopenia and anemia are consistent with vasculitis, whereas hyperfibrinogenemia is consistent with inflammation. Albumin is a negative acute-phase protein, and its concentrations decrease during an inflammatory process; therefore, the hypoalbuminemia identified in our study is consistent with inflammation caused by BTV infection. Protein loss could also be attributable to the vasculitis. Hyperchloremia is attributable to dehydration, whereas metabolic acidosis is secondary to hyperchloremia or hyperlactatemia. The hypokalemia is consistent with anorexia, whereas increased creatine kinase is attributable to perimuscular inflammation from the edema or prolonged periods of recumbency because of lameness.

BTV disease can predispose sheep to secondary bacterial infections; therefore, administration of antimicrobials is recommended. Administration of anti-inflammatory drugs is indicated to reduce inflammation and manage pyrexia. Administration of IV fluids is a supportive therapy to address BTV disease-associated anorexia and hypovolemia. Anorexia might reduce rumen microbe thiamine (vitamin B_1) synthesis; therefore, thiamine supplementation is indicated to prevent polioencephalomalacia. Pantoprazole prevents abomasal ulcerations secondary to stress associated with BTV disease and hospitalization. Furosemide reduces edema associated with vasculitis. Selenium is an antioxidant that enhance reduction of inflammation associated with BTV disease.

Serotypes 10 and 17 are transmitted by *Culicoides sonorensis*.[32] A monovalent attenuated modified live vaccine against serotype 10 is the only vaccine approved for use in sheep in the United States.[18] Experimental infection with serotype 10 in lambs resulted in mild clinical signs of blue tongue disease,[33] whereas an outbreak of blue tongue disease in sheep caused by serotype 17 resulted in a total death rate of 12%.[34] Of the 4 sheep that died, where the serotype was identified in our study, 3 (75%) were diagnosed with BTV serotype 17. Observations in our study suggest differences in the frequency of isolation of different serotypes, severity of signs, and death rate among sheep infected with different BTV serotypes. Vaccine cross-protection among serotypes is rare.[19] Therefore, our results emphasize the need to identify BTV

serotypes for accurate vaccination recommendations because of the mismatch between the available vaccine and the most frequently isolated BTV serotype.

Limitations of our study are limited external validity because the results are from a single institution, and different geographical areas might identify other *Culicoides* species and BTV serotypes. Because of the relatively small number of sheep infected with the different serotypes, we could not determine associations between specific clinical signs or survival and the specific BTV serotypes. Our sample population is biased because it represents sheep exhibiting clinical signs requiring hospitalization and does not include sheep with mild clinical signs. Nonetheless, this study provides valuable and practical information regarding the clinical presentation, management, and outcome of hospitalized sheep with BTV disease.

5 | CONCLUSIONS

Our results indicate the need to perform serotyping of BTV because of the mismatch between the serotype included in the vaccine and the most frequent serotype isolated in clinical cases. The proportion of sheep diagnosed with BTV disease that survive after supportive therapy is relatively high, and the proportion of abortions in BTV-infected pregnant sheep might be low.

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CONFLICT OF INTEREST DECLARATION

Munashe Chigerwe serves as Associate Editor for the *Journal of Veterinary Internal Medicine*. He was not involved in the review of this manuscript. No other authors declare a conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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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