

## Standard Article

*J Vet Intern Med* 2017;31:940–945**Cerebrospinal Fluid Analysis in Recumbent Adult Dairy Cows With or Without Spinal Cord Lesions**

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**Background:** Diagnosis of central nervous system (CNS) lesions in recumbent dairy cattle (RDC) is challenging because neurologic examination is limited and medical imaging often is challenging or unrewarding. Cerebrospinal fluid (CSF) analysis is useful in the diagnosis of CNS disorders in cattle. However, its utility in identifying spinal cord lesions in RDC remains to be evaluated.

**Hypothesis/Objectives:** We hypothesized that CSF analysis would discriminate between RDC with and without spinal cord lesions.

**Animals:** Twenty-one RDC with spinal cord lesions (RDC+) and 19 without (RDC–) were evaluated.

**Methods:** Spinal cord lesions were confirmed at necropsy. Signalment, clinical findings, and CSF results were compared retrospectively. Total nucleated cell count and differential, protein concentration, and red blood cell count in RDC+ and RDC– were compared.

**Results:** Neoplasia, trauma, and infectious processes were the most frequent spinal cord lesions identified. Cerebrospinal fluid protein concentrations and TNCC were significantly higher in RDC+ compared to RDC– ( $P = .0092$  and  $P = .0103$ , respectively). Additionally, CSF protein concentrations and TNCC in RDC– were lower than previously published reference ranges. Using an interpretation rule based on CSF protein concentration and TNCC, it was possible to accurately identify 13 RDC with spinal cord lesions and 6 RDC without lesions. It was not possible to determine spinal cord status in the remaining 18 RDC.

**Conclusions and Clinical Importance:** Cerebrospinal fluid analysis is valuable in the evaluation of spinal cord status in RDC. The prognosis associated with these findings remains to be determined.

**Key words:** Decubitus; Diagnosis; Neurologic; Ruminant.

Spinal cord lesions are a potential cause of recumbency in adult dairy cattle and usually associated with a poor prognosis.<sup>1</sup> Neurologic examination is essential for localizing the anatomic area affected.<sup>2</sup> In large animals, both the neurologic examination and imaging may be more difficult to perform and interpret than in smaller animals. Performing a neurologic examination in a recumbent cow is challenging because gait analysis and postural reactions cannot be evaluated and spinal reflexes may be difficult or impossible to assess accurately. Moreover, use of medical imaging for investigation of spinal cord lesions<sup>3</sup> often is not practical because of size constraints and financial costs. Therefore, a diagnostic tool is needed that may identify spinal cord lesions more reliably in recumbent dairy cattle (RDC).

Cerebrospinal fluid (CSF) is produced by the ventricular system and surrounds the entire central nervous

**Abbreviations:**

CNS	central nervous system
CSF	cerebrospinal fluid
RBC	red blood cell
RDC	recumbent dairy cattle
TNCC	total nucleated count

system (CNS).<sup>4</sup> Cerebrospinal fluid protects the brain from injury and represents a source of nutrition for the brain and spinal cord parenchyma.<sup>5</sup> Collection of CSF from the lumbosacral site in cattle is a simple, safe, and rapid procedure that does not require anesthesia or sedation.<sup>6</sup> Several lesions of the spinal cord are reflected by characteristic variations of CSF composition. For example, neoplastic compression of the spinal cord by an extradural mass in cattle can be associated with an increase in CSF protein concentration.<sup>7</sup> Additionally, CSF eosinophilic pleocytosis recently was found useful in supporting an antemortem diagnosis of *Parelaphostrongylus* spp infection in calves with acute neurologic disease.<sup>8</sup> To our knowledge, no study has specifically investigated the diagnostic value of CSF analysis in RDC.

The purpose of our study was to retrospectively evaluate the diagnostic value of CSF analysis in the identification of spinal cord lesions in RDC. We hypothesized that RDC with spinal cord lesions would have CSF analysis results significantly different from RDC without spinal cord lesions.

**Materials and Methods**

Medical archives from the Farm Animal Hospital of the University Veterinary Hospital Center (CHUV) of the Faculty of Veterinary Medicine in Saint-Hyacinthe (Quebec, Canada) were

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The study was carried out at the veterinary teaching hospital of the University of Montreal.

Preliminary results of this work were presented as a research abstract at the 2014 ACVIM Forum, Nashville, TN.

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searched for the records of all dairy cattle >2 years of age that were referred for recumbency between October 2006 and September 2012. Inclusion criteria included: female, available CSF analysis results and macroscopic and microscopic necropsy reports of the spinal cord. Exclusion criteria included: contradictory information between macroscopic and microscopic findings of the spinal cord in necropsy reports and clinically relevant blood contamination of the CSF. The impact of blood contamination on CSF TNCC and protein concentration was considered minimal when the CSF red blood cell count (RBCC) was <2,000 cells/ $\mu$ L.<sup>9</sup> When the RBCC was >2,000 cells/ $\mu$ L, the contamination was considered clinically relevant and CSF data were excluded from statistical analysis. Clinical and necropsy findings of the RDC group with clinically relevant blood contamination were retained for descriptive statistics.

For each medical record, the following information was retrieved: signalment (age, breed), clinical diagnosis, macroscopic and microscopic necropsy examination results, and CSF analysis results (RBCC, TNCC differential and protein concentration).

Cows were categorized into 2 groups, based on spinal cord examination results described in the necropsy report: RDC without spinal cord damage (RDC-) and RDC with spinal cord damage (RDC+). Based on the necropsy report findings, RDC+ were further subgrouped according to the spinal cord lesion identified on necropsy: infectious, traumatic, or neoplastic. When necropsy lesions were not specific, RDC+ were classified in another subgroup labeled "other." If >1 CSF analysis was performed on a given animal, the results closest to the time of necropsy were used for the study.

Cerebrospinal fluid samples were collected aseptically at the lumbosacral space<sup>10</sup> and placed into tubes containing EDTA for fluid analysis and cytological evaluation (all processed in  $\leq 2$  hours). Red blood cell count and total nucleated cell count (TNCC) were determined using a hemocytometer.<sup>11</sup> One to 4 slides were prepared for cytological evaluation in each case by routine cytocentrifugation of 50–200  $\mu$ L of CSF. All slides were stained with Wright Giemsa. All available slides from each case were retrieved from the archives of the Diagnostic Service and evaluated by a board-certified clinical pathologist (CG) who was blinded to the previous cytology and necropsy examination results. The data recorded from this evaluation included: number of slides available, overall diagnostic quality (acceptable versus nonacceptable) of slides, and a 200-cell differential count (if <200 cells total were present among all available slides, the differential count was based on the total number of cells present). For the differential count, each cell was classified into 1 of the following categories: large mononuclear cell, foamy macrophage, neutrophil, small (nongranular) lymphocyte, granular lymphocyte, reactive lymphocyte, atypical lymphocyte, plasma cell, eosinophil, or "other." Normal CSF reference ranges for this study were based on previously published findings.<sup>9</sup>

### Statistical Methods

Data distribution for all studied variables was non-normal, and consequently, results were reported as median and range (minimum–maximum). Median CSF results (total protein concentration, RBCC, TNCC, differential cell count percentage) between RDC+ and RDC- were compared by a Mann–Whitney–Wilcoxon test. When  $P < .05$ , the result was considered statistically significant. The sensitivity (Se) and specificity (Sp) of CSF protein concentration and TNCC for the detection of spinal cord lesions in RDC were determined. Receiver operating characteristic (ROC) curves were generated (GraphPad Prism 5)<sup>a</sup> and Se and Sp for different cutoff values (with 95% confidence intervals [CI]) were determined.

## Results

Of 395 medical records of RDC that were presented to the farm animal hospital during the study period, 56 met the inclusion criteria. Thirteen cases were excluded because the spinal cord was not examined at necropsy. An additional 3 cases were excluded because of discrepancies between the macroscopic and microscopic descriptions of the spinal cord lesions. Of the remaining cases ( $n = 40$ ), 19 were classified as RDC- and 21 were classified as RDC+.

Holstein was the most common breed of cattle included in this study (36/40, 90%). Other breeds included Red Holstein (3/40, 7.5%) and Ayrshire (1/40, 2.5%). The median age (range) for cattle was 6 (4–10) years for the RDC- group and 5 (2–14) years for the RDC+ group.

Neoplasia was the most frequent postmortem diagnosis found in RDC+ (9/21, 42.9%). The majority of these cases were categorized as neoplastic and attributed to extradural lymphoma ( $n = 7$ ), presumably caused by bovine leukemia virus (BLV). A peripheral nerve sheath tumor was diagnosed in 2 other cows. Infectious causes included epidural abscess ( $n = 2$ ) and nonspecific meningoencephalomyelitis ( $n = 2$ ). Vertebral fracture was the only traumatic cause of lesions in RDC+ ( $n = 4$ ). The nature of the spinal cord lesion was not specific in 4 RDC+, and those cases were classified as "other."

Cerebrospinal fluid analysis was interpretable in 37 RDC. Marked blood contamination of CSF (>2,000 RBCs/ $\mu$ L) was identified in 3 RDC+ with extradural lymphoma. These results were excluded from statistical analysis. Results of CSF analysis are summarized in Table 1.

Clinically relevant blood contamination was not detected in any RDC-. Figures 1, 2 present the distribution of protein concentrations and TNCC in the CSF of RDC+ and RDC-, according to their subgroups. Median concentration of protein in the CSF of RDC+ (0.56 g/L) was significantly higher ( $P = .0092$ ) than median concentration of protein in the CSF of RDC- (0.28 g/L). Total nucleated cell count also was significantly higher ( $P = .0103$ ) in the CSF of RDC+ (4.4 cells/ $\mu$ L) compared to TNCC in the CSF of

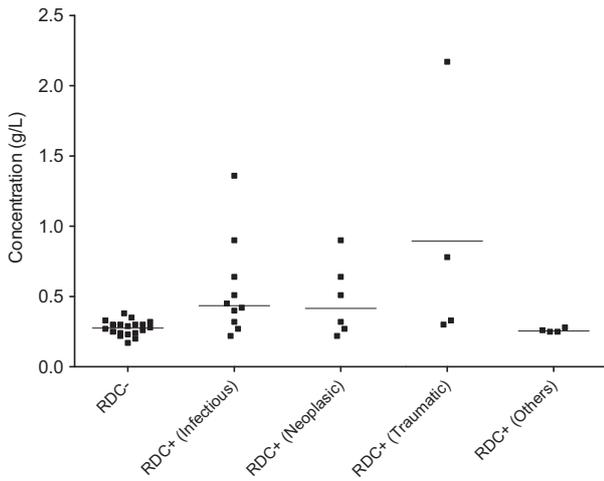
**Table 1.** Cerebrospinal fluid analysis results in RDC with and without spinal cord lesions.

RDC	Protein (g/L)	TNCC (Cells/ $\mu$ L)	RBCC (Cells/ $\mu$ L)
- ( $n = 19$ )	0.28 (0.24–0.30)	0.6 (0–1.6)	7.1 (1.1–25.3)
+ ( $n = 18$ )	0.56* (0.27–0.64)	4.4* (0.6–10.4)	12.7 (1.6–220)

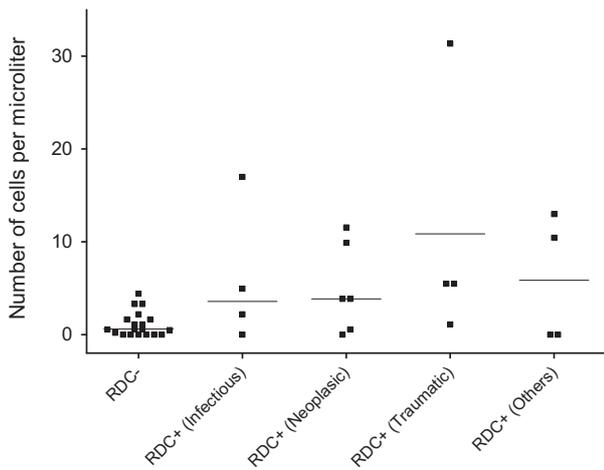
CSF, cerebrospinal fluid; RDC, recumbent dairy cattle; TNCC, total nucleated cell count; RBCC, red blood cell concentration.

A star indicates a statistically significant difference between RDC+ and RDC-.

\* $P < .05$ . Data presented as median with range in italic (minimum–maximum).



**Fig 1.** Cerebrospinal fluid protein concentration in RDC with and without spinal cord lesions. Protein concentrations of RDC with (RDC+) and without (RDC-) spinal cord lesions (scatter plot). The fine horizontal line represents the median of each group. RDC, recumbent dairy cattle.



**Fig 2.** Cerebrospinal fluid total nucleated cell count in RDC with and without spinal cord lesions. Total nucleated cell counts of RDC with (RDC+) and without (RDC-) spinal cord lesions (scatter plot). The fine horizontal line represents the median of each group. RDC, recumbent dairy cattle; TNCC, total nucleated cell count.

RDC- (0.6 cells/μL). No significant difference in RBCC was found between RDC+ and RDC- ( $P = .1959$ , Table 1).

For cytologic evaluation of archived slides, slides from 3/40 RDC were not found in the archives and could not be examined. Of the remaining 37 RDC, slides from 2 cases were determined to be of unacceptable (nondiagnostic) quality. Three cases also were excluded because of marked blood contamination of CSF ( $>2,000$  RBCs/μL). A differential was performed on slides from the remaining 32 RDC. Differential cell counts were not significantly different between RDC+ and RDC- (Table 2).

Based on CSF results, a ROC curve and corresponding table were generated (Figs 3, 4; Tables 3, 4).

Cutoff values that optimized detection of RDC with (RDC+) and without (RDC-) spinal cord lesion were determined on 37 RDC based on analysis of ROC curves. One possible clinical interpretation would be to consider any animal with a CSF protein concentration  $<0.25$  g/L to have a normal spinal cord. Doing so would yield a Se of 94% and Sp of 32%. When CSF protein concentration was  $<0.25$  g/L and TNCC  $\leq 4.5$  cells/μL, Se increased to 100%. Thus, according to our results, RDC with CSF results lower than these cutoffs is unlikely to have spinal cord lesions. On the other hand, CSF protein concentration  $>0.39$  g/L yielded a Se of 50% and Sp of 100% for the presence of a spinal cord lesion. Cerebrospinal fluid TNCC  $>4.5$  cells/μL yielded a Se of 50% and Sp of 100% for the presence of a spinal cord lesion. Thus, according to these guidelines, RDC with CSF protein concentrations  $>0.39$  g/L or CSF TNCC  $>4.5$  cells/μL is likely to have spinal cord lesions. When TNCC is  $\leq 4.5$  cells/μL and protein concentration is between 0.25 and 0.39 g/L, the presence or absence of a spinal cord lesion cannot be reliably predicted. When applying these guidelines to the studied population, accurate diagnosis was achieved for 19 RDC (6 RDC- and 13 RDC+). Spinal cord disease category status remained undetermined for 18 RDC and was distributed as follows: 13 RDC- (72%) and 5 RDC+ (28%).

### Discussion

In our study, analysis of CSF results indicated that protein concentration and TNCC were higher in RDC with spinal cord lesions compared to RDC without spinal cord lesions. By ROC curve analysis, optimal cutoffs were determined and guidelines for interpretation of these results (Table 5) were created. The guidelines are designed to assist in the clinical diagnosis of spinal cord disease (present or absent) in RDC.

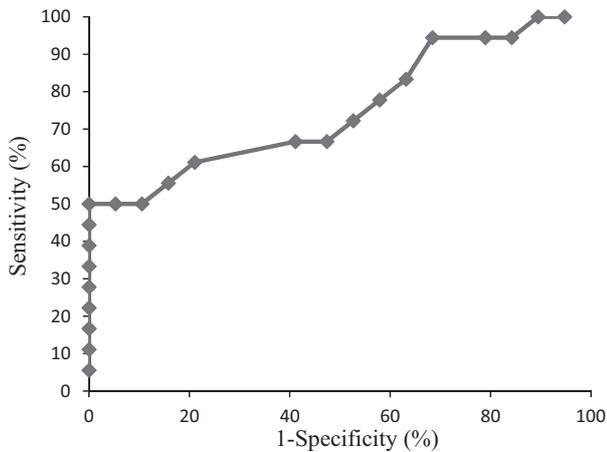
Neoplasia, trauma and infectious processes were the major spinal cord lesions detected in RDC in our study. Increase in CSF protein concentration in RDC+ was mild to moderate. This is a common feature of cattle with spinal cord compression caused by neoplasia.<sup>7</sup> A mild increase in CSF protein concentration of cattle with spinal cord or vertebral body abscesses has also been reported.<sup>12</sup> Finally, a moderate increase in CSF protein concentration has been described in cattle with spinal trauma.<sup>12</sup> Froin's syndrome may be a possible explanation for increased CSF protein concentration in cattle with spinal cord tumors or epidural abscesses. This syndrome, which has been described in humans with spinal cord tumors, represents a blockage of CSF flow in the spinal cord that can result in stagnation of CSF within the thecal sac.<sup>13</sup> The observed increase in CSF protein concentration also may be caused by exudation or transudation from the tumor itself or by hematogenous factors.<sup>14</sup> Froin's syndrome has been proposed as a possible explanation for increased CSF protein concentration in lumbar samples collected from

**Table 2.** Cerebrospinal fluid analysis results for total nucleated cell count and cell differential in RDC with and without spinal cord lesions.

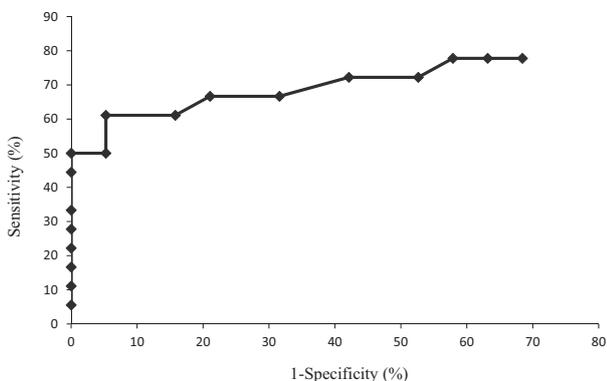
RDC	TNCC (cells/ $\mu$ L)	Neut (%)	Lymp (%)	LMC (%)	LFMC (%)	Eosino (%)	Others (%)
– (17)	0.6 (0–4.4)	0.6 (0–54.6)	39.5 (0–77.2)	35 (5.8–100)	0 (0–19.7)	0 (0–0)	0 (0–6.8)
+ (15)	5.0 (0–31.35)	0 (0–24)	37.1 (20–100)	44 (0–68.5)	1.5 (0–26)	0 (0–4.5)	0 (0–58)

CSF, cerebrospinal fluid; RDC, recumbent dairy cattle; TNCC, total nucleated cell count; Neut, neutrophil; Lymp, lymphocyte; LMC, large mononuclear cell; LFMC, large foamy monocytooid cell; Eosino, eosinophil.

Data presented as median (range; minimum–maximum). This table represents data collected following evaluation of 32/37 archived CSF slides.



**Fig 3.** Receiver operating characteristic curve data of cerebrospinal fluid protein concentration in recumbent dairy cattle with and without spinal cord lesions. The sensitivity (Se) and specificity (Sp) of cerebrospinal fluid protein concentration for the detection of spinal cord lesions was determined by ROC curve analysis. ROC curves were generated, and Se and Sp for different cutoff values (with 95% confidence intervals [CI]) were determined. ROC, receiver operating characteristic.



**Fig 4.** Receiver operating characteristic curve data of cerebrospinal fluid total nucleated cell count in recumbent dairy cattle with and without spinal cord lesions. The sensitivity (Se) and specificity (Sp) of cerebrospinal fluid total nucleated cell count concentration for the detection of spinal cord lesions was determined by ROC curve analysis. ROC curves were generated, and Se and Sp for different cutoff values (with 95% confidence intervals [CI]) were determined. ROC, receiver operating characteristic.

sheep with thoracolumbar epidural abscesses.<sup>15</sup> Finally, local antibody production within the CNS, as documented in horses with equine protozoal myeloencephalitis,<sup>16</sup> may contribute to increased CSF protein concentration.

Increased TNCC in the CSF of RDC+ often was mild, making prediction of spinal cord condition difficult. For example, TNCC of CSF of cattle with spinal lymphoma often is normal and neoplastic cells usually are not observed.<sup>7,12</sup> However, a mild mononuclear pleocytosis is considered a characteristic finding in cattle with spinal abscesses or trauma.<sup>12</sup> In 1 retrospective study that evaluated 66 cattle with CNS disorders, all cattle with infectious causes, including vertebral body abscesses, had CSF pleocytosis.<sup>17</sup> Additionally, cattle with chronic infections tended to have a higher percentage of macrophages in the CSF. Finally, cattle with acute CNS trauma often have pleocytosis associated with increased RBCC and erythrophagocytosis.<sup>17</sup>

Another interesting finding of our study concerns protein concentration and TNCC in the CSF of RDC–. Composition and analysis of CSF in clinically normal adult cattle previously has been reported.<sup>9</sup> The TNCC reported in that study ranged from 0 to 9 cells/ $\mu$ L (mean, 2.88 cells/ $\mu$ L). The cells consisted mostly of lymphocytes and the protein concentration ranged from 23.4 to 66.3 mg/dL (mean, 39.2 mg/dL). In our study, RDC– had a lower CSF protein concentration and TNCC compared to the 16 clinically normal adult cattle in the study cited. The number of cattle included in both studies and the ages of the animals were similar. Interestingly, the previous study found that beef cows ( $n = 5$ ) had higher CSF protein concentration than did dairy cows ( $n = 11$ ).<sup>9</sup> Also of interest, none of the cattle sampled in the cited study were recumbent. Recumbency possibly could influence CSF flow and therefore modify CSF composition. Our results suggest that CSF reference values for protein concentration and TNCC in RDC without spinal lesions may be lower than previously reported.

Blood contamination of CSF during collection can interfere with CSF analysis. In cattle, blood contamination of CSF  $<2,000$  RBC/ $\mu$ L has been found to alter CSF protein concentration minimally.<sup>9</sup> In that same study, a statistically significant relationship between RBCC and neutrophil and lymphocyte counts was not observed.<sup>9</sup> Because CSF samples with  $>2,000$  RBC/ $\mu$ L were excluded from our study, the effect of blood

**Table 3.** Sensitivity and specificity for different cutoff values for cerebrospinal fluid protein concentration in the recumbent dairy cattle.

Cutoff, g/L	Sensitivity, %	95% Confidence Intervals (CI)	Specificity, %	95% CI	Likelihood Ratio
>0.1850	100	81.47–100.0	5.263	0.1332–26.03	1.06
>0.2100	100	81.47–100.0	10.53	1.301–33.14	1.12
>0.2250	94.44	72.71–99.86	15.79	3.383–39.58	1.12
>0.2350	94.44	72.71–99.86	21.05	6.052–45.57	1.2
>0.2450	94.44	72.71–99.86	31.58	12.58–56.55	1.38
>0.2550	83.33	58.58–96.42	36.84	16.29–61.64	1.32
>0.2650	77.78	52.36–93.59	42.11	20.25–66.50	1.34
>0.2750	72.22	46.52–90.31	47.37	24.45–71.14	1.37
>0.2850	66.67	40.99–86.66	52.63	28.86–75.55	1.41
>0.2950	66.67	40.99–86.66	57.89	33.50–79.75	1.58
>0.3100	61.11	35.75–82.70	78.95	54.43–93.95	2.9
>0.3250	55.56	30.76–78.47	84.21	60.42–96.62	3.52
>0.3400	50	26.02–73.98	89.47	66.86–98.70	4.75
>0.3650	50	26.02–73.98	94.74	73.97–99.87	9.5
>0.3900	50	26.02–73.98	100	82.35–100.0	
>0.4100	44.44	21.53–69.24	100	82.35–100.0	
>0.4350	38.89	17.30–64.25	100	82.35–100.0	
>0.4800	33.33	13.34–59.01	100	82.35–100.0	
>0.5750	27.78	9.695–53.48	100	82.35–100.0	
>0.7100	22.22	6.409–47.64	100	82.35–100.0	
>0.8400	16.67	3.578–41.42	100	82.35–100.0	
>1.130	11.11	1.375–34.71	100	82.35–100.0	
>1.765	5.556	0.1406–27.29	100	82.35–100.0	

**Table 4.** Sensitivity and specificity for different cutoff values for cerebrospinal fluid total nucleated cell count in recumbent dairy cattle.

Cutoff, Cells/ $\mu$ L	Sensitivity, %	95% Confidence Intervals (CI)	Specificity, %	95% CI	Likelihood Ratio
>0.1000	77.78	52.36–93.59	31.58	12.58–56.55	1.14
>0.3500	77.78	52.36–93.59	36.84	16.29–61.64	1.23
>0.5250	77.78	52.36–93.59	42.11	20.25–66.50	1.34
>0.5750	72.22	46.52–90.31	47.37	24.45–71.14	1.37
>0.8500	72.22	46.52–90.31	57.89	33.50–79.75	1.72
>1.375	66.67	40.99–86.66	68.42	43.45–87.42	2.11
>1.925	66.67	40.99–86.66	78.95	54.43–93.95	3.17
>2.750	61.11	35.75–82.70	84.21	60.42–96.62	3.87
>3.575	61.11	35.75–82.70	94.74	73.97–99.87	11.61
>4.125	50	26.02–73.98	94.74	73.97–99.87	9.5
>4.675	50	26.02–73.98	100	82.35–100.0	
>5.225	44.44	21.53–69.24	100	82.35–100.0	
>7.700	33.33	13.34–59.01	100	82.35–100.0	
>10.18	27.78	9.695–53.48	100	82.35–100.0	
>11.00	22.22	6.409–47.64	100	82.35–100.0	
>12.28	16.67	3.578–41.42	100	82.35–100.0	
>15.00	11.11	1.375–34.71	100	82.35–100.0	
>24.18	5.556	0.1406–27.29	100	82.35–100.0	

contamination on results is assumed to be minimal. Interestingly, the 3 cases that were excluded on the basis of CSF RBCC  $>2,000$  RBC/ $\mu$ L were diagnosed with extradural lymphoma in the lumbosacral space at necropsy. However, 1 study that examined CSF results of cattle with compressive neoplasms affecting the spinal cord<sup>7</sup> did not report increased CSF RBCC. Although results from CSF samples with clinically relevant blood contamination should be interpreted with caution, these

samples should not be discarded. Instead, they should be carefully examined for atypical or neoplastic lymphocytes and other potentially clinically relevant findings.

Our study had some limitations. First, the prognosis associated with spinal cord lesions in RDC could not be determined. In general, the presence of a spinal cord lesion of any kind in RDC is considered to be a negative prognostic factor. Additionally, extrapolation of

**Table 5.** Interpretation rules for clinical classification of RDC based on cerebrospinal fluid protein concentration and total nucleated cell count.

	Protein (g/L)		
	P < 0.25	0.25 ≤ P ≤ 0.39	P > 0.39
TNCC			
≤4.5	RDC–	Inconclusive	RDC+
>4.5	RDC+	RDC+	RDC+

RDC+, recumbent dairy cattle with spinal cord lesion; RDC–, recumbent dairy cattle without spinal cord lesion; P, protein; TNCC, total nucleated cell count.

the data from our study to other bovine populations should be performed with caution. For example, the proposed interpretation rules (Table 5) might not be applicable to standing cattle or beef cattle. As previously mentioned, higher CSF protein concentration in healthy beef cattle compared to healthy dairy cattle has been observed.<sup>9</sup>

In conclusion, significant differences in CSF protein concentration and TNCC were found between RDC with and without spinal cord lesions. Analysis of these differences facilitated the development of interpretation guidelines that likely will help clinicians predict the presence or absence of spinal lesions in these patients. The prognosis associated with the suggested guidelines remains unknown.

### Footnote

<sup>a</sup> GraphPad Prism Statistical Software, version 5, GraphPad Software Inc, San Diego, CA

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*Conflict of Interest Declaration:* Authors declare no conflict of interest.

*Off-label Antimicrobial Declaration:* Authors declare no off-label use of antimicrobials.

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