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Original Article
Livestock Diseases

Association between the severity of lung lesions and performance, mortality, first conception, and pneumonia treatment in dairy calves[1]

João P. Andrade[2], Bárbara A. Alves[3]*, Gabriela Anteveli[3], Matheus F. Serafini[4], Paulo R.O. Paes[3], Tiago F. Moreira[3], Rodrigo M. Meneses[3], Elias J. Facury Filho[3], Antônio U. Carvalho[3]

ABSTRACT.- Andrade JP, Alves BA, Anteveli G, Serafini MF, Paes PRO, Moreira TF, Meneses RM, Facury Filho EJ, Carvalho AU. **Association between the severity of lung lesions and performance, mortality, first conception, and pneumonia treatment in dairy calves.** *Pesquisa Veterinária Brasileira 45:e07636, 2025*. Departamento de Clínica e Cirurgia Veterinárias, Escola de Veterinária, Universidade Federal de Minas Gerais, Campus Pampulha, Av. Antônio Carlos 6627, Cx. Postal 567, Belo Horizonte, MG 31270-901, Brazil. E-mail: balves@ufmg.br

The objectives of this study were to determine the impact of lung lesions in dairy calves on weight gain throughout the pre-weaning phase, mortality until 19 months of age, and age at first conception, and its association with transfer of passive immunity (TP) and diarrhea and establish the efficiency of on-farm calf pneumonia diagnosis. Thoracic ultrasonography (TUS) was conducted on 193 Holstein calves aged 1 to 24 weeks, and data related to TP, diarrhea, weight gain, and age at first conception were collected. Out of these, 109 calves were used to compare TUS findings with on-farm diagnosis, which was based on treatment records. For each unit increase in plasma protein (TP) above 5.0 g/dL, there was a reduction in the number of lesions > 1 cm (R^2 = 0.0061; *P* = 0.003) and cases treated for pneumonia (R^2 = 0.021; *P* = 0.044), whereas more days in diarrhea represented more treatments (R^2 = 0.022; *P* = 0.04). The number of intercostal spaces (ICS) affected had a negative effect on the time required to reach a body weight of 370 kg (R^2 = 0.025; *P* = 0.001) and an increase in the mean value of the number of ICS with consolidations > 1 cm by one unit resulted in a 51% increase in the death rate (hazard ratio = 1.51; *P* = 0.002) up to 19 months of age. In the comparison of TUS and on-farm diagnosis, 36.69% (40/109) of the calves were misdiagnosed. These results underscore the importance of enhancing diagnostic methods and strategies for pneumonia in calves, as well as identifying and mitigating associated risk factors to improve health, future productivity, and survival.

INDEX TERMS: Thoracic ultrasonography, lung consolidation, transfer of passive immunity, survival rate, calves.

RESUMO.- [**Associação entre severidade de lesões pulmonares e desempenho, mortalidade, primeira concepção e tratamento de pneumonia em bezerros leiteiros.**] Os objetivos deste estudo foram determinar o impacto das lesões pulmonares em bezerros leiteiros no ganho de peso ao longo da fase de aleitamento, na mortalidade até os 19 meses de idade e na idade a primeira concepção, e sua associação com a transferência de imunidade passiva (TIP) e diarreia, e estabelecer a eficiência do diagnóstico de pneumonia em bezerras na fazenda. Ultrassonografia torácica (UST) foi realizada em 193 bezerras Holandês com idade entre um e 24 semanas, e foram coletados dados relacionados a TIP, diarreia, ganho de peso e idade a primeira concepção. Destas, 109 bezerras foram utilizadas para comparar os resultados de UST com o diagnóstico na fazenda, que foi baseado em registros de tratamento. Para cada aumento unitário de proteína plasmática (PPT) acima de 5,0 g/dL, houve redução

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[2] Centro Universitário Newton Paiva, Belo Horizonte, MG, Brazil.

[3] Departamento de Clínica e Cirurgia Veterinárias, Escola de Veterinária, Universidade Federal de Minas Gerais (UFMG), Campus Pampulha, Av. Antônio Carlos 6627, Cx. Postal 567, Belo Horizonte, MG 31270-901, Brazil. *Corresponding author: balves@ufmg.br

[4] Secretaria da Agricultura, Pecuária, Produção Sustentável e Irrigação, Porto Alegre, RS, Brazil.

no número de lesões > 1 cm (R^2 = 0,0061; *P* = 0,003) e de casos tratados para pneumonia (R^2 = 0,021; *P* = 0,044), enquanto mais dias de diarreia representaram mais tratamentos (R^2 = 0,022; *P* = 0,04). O número de espaços intercostais (EIC) afetados teve efeito negativo no tempo necessário para atingir o peso corporal de 370 kg (R^2 = 0,025; P = 0,001) e aumento no valor médio do número de EIC com consolidações > 1 cm em uma unidade resultou em um aumento de 51% na taxa de mortalidade (hazard ratio = 1,51; *P* = 0,002) até os 19 meses de idade. Na comparação entre UST e diagnóstico na fazenda, 36,69% (40/109) das bezerras foram mal diagnosticadas. Estes resultados ressaltam a importância de melhorar os métodos e estratégias de diagnóstico para a pneumonia em bezerras, bem como identificar e mitigar os fatores de risco associados para melhorar sua saúde, produtividade futura e sobrevivência.

TERMOS DE INDEXAÇÃO: Ultrassonografia torácica, consolidação pulmonar, transferência de imunidade passiva, taxa de sobrevivência, bezerros.

INTRODUCTION

Among the infectious diseases that comprise the bovine respiratory disease complex (BRD), pneumonia is considered the most significant; among these, bacterial bronchopneumonia is the most important for dairy calves. Late and/or incorrect diagnoses performed in the field pose major challenges in controlling their occurrence, potentially leading to significant losses for animals, both in the short (impaired weight gain) and long term (delayed age at first conception, impaired milk production at first lactation, and diminished survival rates at the end of first lactation) (Stanton et al. 2012, Teixeira et al. 2017, Dunn et al. 2018). In recent years, there has been growing emphasis on the development of more efficient diagnostic methods for pneumonia in cattle. One promising technique that has shown positive results in terms of diagnosis, prognosis, and monitoring of pneumonia is thoracic ultrasonography (Rabeling et al. 1998, Ollivett & Buczinski 2016). This diagnostic approach focuses primarily on the identification and measurement of lung consolidation. Moreover, the extent of the lesion can serve as an indicator of pneumonia, regardless of whether the animal exhibits clinical signs (Rabeling et al. 1998, Reinhold et al. 2002, Ollivett & Buczinski 2016). Currently, clinical presentation is widely employed as the primary diagnostic tool in the field. Nonetheless, relying solely on it for diagnosis may lead to ineffective treatment, as the success of treatment depends on early detection of lung lesions, and 10 to 90% of pneumonia cases present as subclinical (Buczinski et al. 2014, Gouda 2015, Ollivett & Buczinski 2016). Comparing the treatment success rate for pneumonia on farms with the detection of lung lesions through thoracic ultrasonography provides valuable insights into the quality of the diagnostic practices employed on farms. Additionally, weight gain and reproductive indices in animals with and without lung lesions at weaning have been used to measure the long-term impact of unresolved pneumonia cases on cattle productivity. However, studies investigating the effects of lesions of varying severities on the productive and reproductive performance of dairy cows are limited in Brazil. In recent years, studies in the US and Ireland showed a decrease in the mean average daily gain (ADG) of 0.63 kg/d and 0.21 kg/d, respectively, in calves with lung consolidation ≥ 1 cm^2 compared with calves with no consolidation (Cramer & Ollivett 2019, Rhodes et al. 2021). Another study in Iran, with a higher threshold of ≥ 3 cm for lung consolidation, concluded that calves with consolidation had significantly lower ADG compared with animals with no consolidation. However, with a threshold of ≥ 1 cm, this difference was only observed in cases where the consolidation remained for longer periods (Sáadatnia et al. 2023). Despite these promising results, several factors could influence ADG, so its association with thoracic ultrasonography (TUS) should be tested across different scenarios to better isolate the real effect of lung consolidation on growth and weight gain. The impairment of these factors has been shown to affect later-life productivity. It is likely the primary cause of the referred link between lung lesions in the preweaning phase and reduced productive and reproductive indices in cattle later in life.

Although it is challenging to pinpoint individually, various risk factors have been implicated in disrupting the equilibrium of the nasopharyngeal microbiota, thus promoting bacterial bronchopneumonia in cattle (Ackermann et al. 2010). In this study, we focused on two potential causes contributing to the increased risk of developing bronchopneumonia in the monitored farm: failure in passive immunity transfer and diarrhea.

Newborn calves have an immature immune system, and due to the nature of the species' placenta, they are agammaglobulinemic. Consequently, their initial immune protection relies heavily on the passive transfer of maternal immunoglobulins (IgA, IgM, and IgG) through colostrum within the first few hours of life (Shivley et al. 2018). The failure in the transfer of passive immunity (TPI) in calves has been associated with lower ADG and higher morbidity and mortality rates (Godden et al. 2019). A recent German study found an association between poor (< 8.1% Brix) TPI and a greater hazard ratio (HR) for pneumonia, overall morbidity and mortality in comparison with excellent (≥ 9.4% Brix) TPI, as well as an association between fair (8.1–8.8% Brix) and good (8.9–9.3% Brix) TPI and a greater hazard ratio (HR) for pneumonia, overall morbidity and mortality in comparison with excellent TPI (Sutter et al. 2023). Other than this direct effect, TPI can also be related to higher diarrhea morbidity (Sutter et al. 2023), which results in the loss of electrolytes, water, and nutrients through feces (Naylor 1989, Freitas et al. 2010). All these factors can have a negative impact on various organic functions (Carlson & Bruss 2008), including immune responses and ciliary beating of the mucociliary apparatus in the respiratory tract, increasing susceptibility to respiratory infections (Bartlett et al. 2008, Linden et al. 2008).

Our hypotheses posit that the greater the extent of lung lesions identified using thoracic ultrasonography, the more compromised the performance and the higher the age at first conception of heifer calves. Furthermore, the occurrence of bovine respiratory disease can be associated with the failure of passive immunity transfer and the presence of diarrhea. Therefore, the objectives of this study were to determine the impact of lung lesions in dairy calves on weight gain throughout the pre-weaning phase, mortality until 19 months of age and age at first conception, and its association with transfer of passive immunity and diarrhea, as well as establish the efficiency of on-farm calf pneumonia diagnosis.

MATERIALS AND METHODS

Ethical approval. The study was approved by the Ethics Committee in the Use of Animals of the "Universidade Federal de Minas Gerais" (UFMG) (protocol number 358/2019).

Population. The study was conducted on a commercial dairy farm with an intensive system located in the Midwest region of Brazil from March 2019 to September 2020. The property had a predominantly Holstein herd, with approximately 944 animals in lactation, with an average milk production of 29 kg/d per cow and an average of 60 calvings per month. A total of 193 calves were enrolled in this study during the first week of life. At the beginning of the experiment, all heifers aged less than 70 days and those born within the next 40 days were used. The monitoring of these animals took place over 128 days.

The property had a predominantly Holstein cattle herd. The cows were reared in a Free Stall system, and births took place in maternity stalls attached to the facilities where the cows were kept.

Calf rearing practices and housing. After birth, calves were transported to a facility consisting of a shed open on the sides and with natural ventilation, where they received colostrum with at least 24% of Brix in a volume corresponding to 15% of body weight distributed during the first six hours of life via a feeding bottle. Subsequently, 6 L of pasteurized transition milk was provided daily until 72 hours of life.

Calves were individually housed until weaning in 2 m^2 suspended cages with straw bedding and a flushing system to remove manure. Concentrate and water were provided *ad libitum*. The liquid diet consisted of 6 L of pasteurized waste milk up to 40 days of age, corrected for dry matter with milk replacer to 13%, and then 6 L of milk replacer diluted to 13% dry matter. Weaning began after 60 days of life when the animals had reached a minimum weight of 80 kg. Thereafter, 3 L of milk replacer was provided in the morning for 15 days.

Subsequently, the animals remained, on average, for another 10 days in this shed until they left for the post-weaning sector. The animals were then kept in paddocks, in groups ranging from eight to 10 animals up to 150 days of life, and later in groups of 30 animals.

Calves were not vaccinated against respiratory pathogens; however, cows were vaccinated 60 days before parturition with a vaccine dose against *Salmonella* Dublin, *Salmonella* Typhimurium, and *Pasteurella multocida* ("Vacina Contra a Pasteurelose e Salmonelose Bovina Labovet", Labovet®).

Data collection. Thoracic ultrasonography (TUS) was performed at 1st, 4th, 6th, 8th, 10th, 12th, 16th, 20th and 24th weeks of life on the calves born after the initiation of the study. Heifers aged less than 70 days at the beginning of the study and that were enrolled in it had missing evaluations according to the age of entrance. In total, 328 evaluations were carried out in the Initial Calf Housing phase (IH; 1st to 6th week of life); 539 in the Final Calf Housing phase (FH; 8th to 12th week), totaling 887 evaluations of pre-weaned animals that were grouped as General Calf Housing (GH, 1st to 12th weeks); 291 in Post-weaning (PW, from 16th to 24th week) and 1,158 in Total Assessments (TA, 1st to 24th week) (Table 1).

In addition, information was collected from farm records on treatments for diseases carried out until weaning, cases of diarrhea up to 20 days of age, and transfer of passive immunity.

Diarrhea was monitored daily. Visual evaluation of the calves' feces until 20 days of age was performed by a staff member in the morning. Diarrhea was classified as follows: normal = when they were pasty to firm; mild diarrhea = despite being pasty, tended to drip; moderate diarrhea = liquid feces with some pasty portions; and severe diarrhea = completely fluid feces (Freitas et al. 2010). All cases of neonatal diarrhea on the farm were treated with 2.5 mg/kg of Enrofloxacin orally once a day for three days.

The transfer of passive immunity (TPI) was determined by measuring plasma protein levels in calves between two and five days after birth through optic refractometry. It was performed by farm personnel, and the data were later obtained from farm records. The possible effect of cow vaccination prior to birthing on TPI was not evaluated.

Thoracic ultrasonography. Thoracic ultrasonography was performed by a single trained veterinarian using a Kaixin KX 5100 ultrasound model, with a transrectal linear transducer at a frequency of 6.5 MHz, with an image depth of 10 cm in B-mode, and 70% alcohol

Table 1. Distribution of thoracic ultrasonography evaluations according to the start and end of evaluations in a group of 193 Holstein calves up to the 24th week of life on an intensive dairy farm located in the Midwest region of Brazil

Number of calves	Weeks of life								
	1st	4th	6th	8th	10th	12th	16th	20th	24th
28	-	-	-	-	28	28	27	26	26
23	-	-	-	23	23	22	23	20	18
8	-	-	8	8	8	8	8	7	8
13	-	-	13	13	12	13	13	12	-
33	-	33	33	33	33	31	29	25	-
57	40	56	56	56	55	54	49	-	-
31	27	31	31	31	31	29	-	-	-
TOTAL = 193	67	120	141	164	190	185	149	90	52
Total evaluations by period									
IH	328								
FH			539						
GH	867								
PW						291			
TA	1.158								

Columns: number of evaluations per week of life; Rows: subgroup of calves according to the week they started and ended their evaluations; Evaluations per period: IH = initial calf housing from 1st to 6th week of life, FH = final calf housing from 8th to 12th week, GH = general calf housing from 1st to 12th week, PW = post-weaning from 16th to 24th week, TA = total assessments from 1st to 24th week.

as a conductor. A normal lung was considered when in the presence of reverberation artifacts or "A-lines," characterized by parallel and hyperechoic bands starting from the pleura. "Comet tails" or "B-lines" were represented by hyperechoic bundles perpendicular to the pleura region. Pulmonary consolidation areas were defined as any lung portion without reverberation, presenting hypoechoic and hyperechoic characteristics from the pleura. Pleural effusion was identified by the presence of an anechoic portion between pleurae. The changes were recorded according to their location in the intercostal space, and the consolidations were measured according to their depth using the ultrasound's measure function in the static image (Ollivett & Buczinski 2016). Based on the ultrasonographic changes, the animals were classified according to a previously proposed Ultrasonography Scoring system that considered a 5-point scale after examining the five lung lobes separately: calves were given a score of 0 if only reverberation artifacts, few comet tails, and consolidations < 1 cm were present; score 1, for diffuse comet tails occupying one or more lung lobes; score 2, for pulmonary consolidations > 1 cm that did not occupy the entire lung lobe; score 3, for complete consolidation of one lung lobe; score 4, for complete consolidation of two lung lobes; and score 5, for complete consolidation of three or more lung lobes. Calves were considered positive for pneumonia on thoracic ultrasonography when they presented a score of ≥ 1 (Cramer & Ollivett 2019).

Treatment for pneumonia. Pneumonia treatment was carried out by an employee trained by the farm, following a diagnosis made by them through daily animal inspections and based on an evaluation of behavior, breathing pattern, cough, nasal secretion, rectal temperature, and pulmonary auscultation. Calves were treated if there was an increased breathing pattern, and/or presence of cough, and/or presence of nasal secretion, and/or alterations in pulmonary auscultation. Behavior and rectal temperature were used as auxiliary data.

The therapeutic protocols were established by the farm veterinarian and included two applications with 48 hours interval of 15 mg/kg of body weight of Amoxicillin Trihydrate, intramuscularly, as the first choice; as the second choice, two applications of florfenicol were used, 20 mg/kg of body weight, intramuscularly, with 48 hours interval; and as the third choice, 10 mg/kg of body weight of Tilmicosin was administered subcutaneously behind the shoulder. If, at the end of treatment with the first-choice antimicrobial, the calves still presented with clinical signs corresponding to pneumonia, the second-choice antimicrobial protocol was implemented, and the same was valid for the third-choice antimicrobial after that.

After the ultrasonographic examination, the animals that presented pulmonary consolidations were informed to the assigned employee, enrolled in their routine evaluation for diagnosis, and treated for pneumonia following the criteria described above (based on clinical observation).

In the analysis, it was considered a new treatment for pneumonia those that had elapsed at least 15 days after the last treatment was performed. The number of treatments performed until weaning was obtained from farm records.

Weight gain, survival, and first conception. Weight gain was evaluated by inferring the thoracic perimeter just behind the scapula, passing through the sternum and the spinal processes of the thoracic vertebrae. A conventional scale for weighing dairy cattle was used to observe the predetermined weight for large breeds. The first weighing was at birth, followed by weighing coinciding with TUS assessments and at 13 months of life, following the farm protocol to determine the animals' entry into reproduction (the farm adopted a minimum weight of 370 kg and a minimum age of 13 months to do so). Weight gain (average daily gain – ADG considered the entire evaluation period for each calf) was obtained from farm records and weighing coinciding with TUS assessments. The age to reach 370 kg, the number of inseminations necessary for first conception, and deaths up to 19 months of age were obtained from farm records.

Statistical analysis. The sample size was calculated according to the 8.9% prevalence of pulmonary consolidations reported by Buczinski et al. (2018) in suckling calves and considering a type I error of 5% and the expected margin of error of 4%.

To evaluate the association between two quantitative (i.e., numerical) variables, regression models were performed, the significance of the regression and the coefficient of determination were calculated, and the equation of the regression line was estimated. This was used to relate the number of intercostal spaces with consolidations > 1 cm on ultrasonography and the number of cases treated for pneumonia in the Initial Calf Housing phase (IH – 1st to 6th week of life), Final Calf Housing phase (FH – 8th to 12th week), General Calf Housing (GH – 1st to 12th week), Post-weaning (PW – 16th to 24th week), and Total Assessments (TA – 1st to 24th week), as well as weight gain. Also, this analysis was used to determine the association between days of diarrhea and treatments for pneumonia.

To evaluate the effect of the number of intercostal spaces > 1 cm on the survival of the animals, the average value of all evaluations carried out over time in the same animal was calculated to obtain a single value. The effect of increasing the average value on the survival of the animals was evaluated by adjusting the regression models of Proportional Failure Rates or the Cox Semiparametric Model (Cox 1972).

All analyses were performed using the software R version 3.6.2 (R Core Team 2019).

RESULTS

Relationship between respiratory disease, weight gain, first conception, and mortality

Average daily weight gain was negatively associated with an increase in the number of intercostal spaces with lesions > 1 cm during the IH (y = 0.63-0.044x; R^2 = 0.05, P = 0.002), GH (y = 0.85-0.038x; R^2 = 0.027; P = 0.011), PW (y = 0.86-0.055x; R^2 = 0.02; P = 0.02), and TA (y = 0.86-0.04x; R^2 = 0.025; P = 0.001) periods. The number of intercostal spaces with lesions > 1 cm had a positive effect on the time taken to reach a weight of 370 kg (R^2 = 0.12; P = 0.001) (Fig. 1).

For the investigation of the effect of respiratory disease in the first six months of life and conception, data from 119 heifers that were pregnant at the last herd data collection were evaluated, and on average, 1.98 inseminations (1-6; Standard deviation – SD 1.17) were required to become pregnant. There was no evidence of a relationship between the average number of intercostal spaces with consolidations > 1 cm (P = 0.613) or the number of pneumonia cases during the pre-weaning period (P = 0.471) and conception of the first pregnancy.

Of the 193 calves evaluated, 51 left the herd until 19 months of age. The mortality rate was 4.1% (8/193) up to three months of age, and only one animal died of pulmonary complications. From three to 19 months of age, the observed mortality was 23.2% (43/185), and pneumonia was responsible for 30.2% (13/43) of the deaths during this period. These diagnoses were obtained by necropsy performed by an experienced veterinarian. Four of the calves that died presented with score 1 ate the TUS (diffuse comet tails occupying one or more lung lobes), and microbiological diagnosis confirmed

the presence of *Salmonella* Dublin (swab samples of the lesions were cultivated in a selective medium and serotyping was performed). All heifers that died from pneumonia had at least one positive ultrasonographic examination during the study. In the Cox regression analysis, when the mean value of the number of intercostal spaces with consolidations > 1 cm increased by one unit, the death rate increased by an average of 51% (hazard ratio = 1.51; 95% CI (1.16-1.97; P = 0.002) up to 19 months.

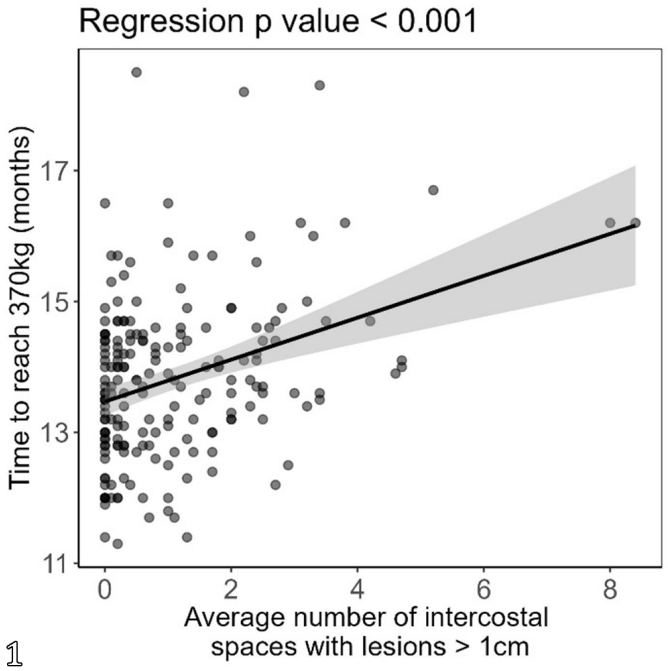

Fig. 1. Relationship between the average number of intercostal spaces with pulmonary consolidations > 1 cm, evaluated through thoracic ultrasonography from the first to the 24th week of life, and the time to reach 370 kg in a group of 193 Holstein calves in an intensive dairy farm located in the Midwest of Brazil.

Number of pneumonia cases treated during the pre-weaning period and their relationship with thoracic ultrasonography, transfer of passive immunity, and days with diarrhea

During the study, it was found that 74% (142/193) of the calves were treated for pneumonia until weaning. Of these, 43.6% (62/142) underwent only one protocol of antibiotic therapy, 26.7% (38/142) underwent two, 14.8% (20/142) underwent three, 8.4% (12/142) underwent four, and 7.7% (11/142) underwent five or more protocols.

The number of treated pneumonia cases varied over time (Fig. 2). A peak was observed in the fourth week of life, with a gradual decrease from week six to the twelfth week.

Pneumonia treatments occurred both following the farm employee's diagnosis through clinical sign observation and after a positive ultrasonography examination. To understand the association between pneumonia treatment performed on the farm and ultrasonography examination, 109 calves were examined. These animals were selected because they underwent all evaluations performed between the 4th and 12th week of life. The 12th-week evaluation was used to verify whether the animal had recovered from lung injuries, that is, whether it did not present any further lung consolidation on ultrasonography examination. Therefore, animals that presented with only one positive evaluation on ultrasonography at the 12th week of life and had no history of treatment before the 10th week of life evaluation were excluded from this analysis. As a result, it was observed that 15% (17/109) of the calves did not receive any treatment for pneumonia (Fig. 2). However, 47% (8/17) of these calves presented with lung consolidations on ultrasonography examination of at least one evaluation, and 25% (2/8) of the calves in this situation had an ultrasonography score of 3. In the last evaluation, 75% (6/8) of untreated calves with at least one positive evaluation returned to negative on ultrasonography examination.

The remaining calves, 84.4% (92/109), were treated for pneumonia. Of these, 65.2% (60/92) had at least one positive evaluation on ultrasonography during the treatment period,

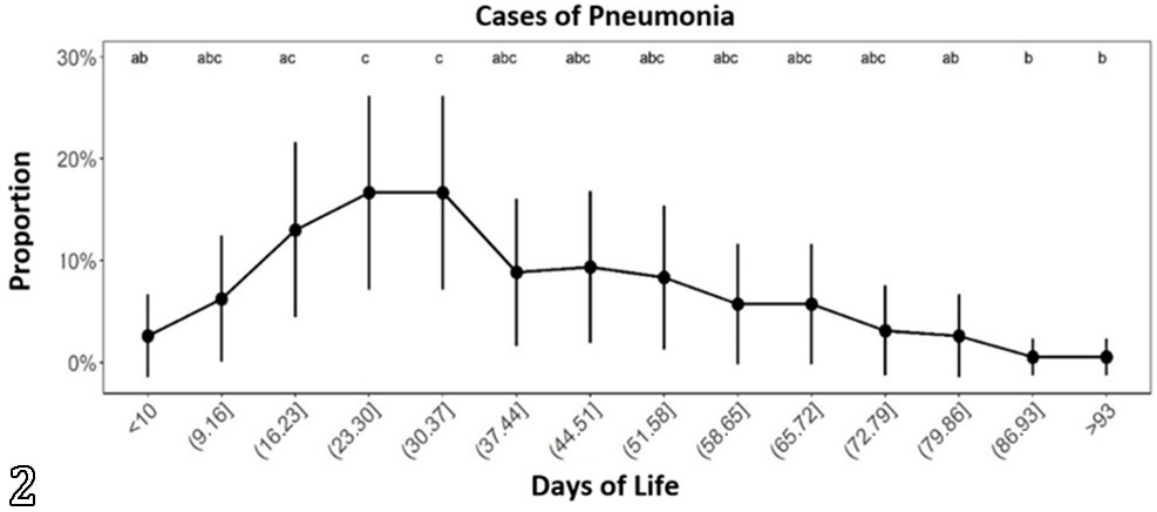

Fig. 2. Frequency of pneumonia cases treated after diagnosis by a farm employee in a group of 193 Holstein calves evaluated from birth to weaning on a dairy farm located in the Midwest region of Brazil. Lowercase letters indicate the differences in pneumonia frequency between the times. Groups that share at least one letter are not significantly different from each other (P < 0.05).

and recovery was observed in 45% (27/60) of the cases. In the group of calves that recovered, 29.6% (8/27) had a score > 3 on the first ultrasonography examination near the day of treatment, 44.4% (12/27) had at least three positive examinations, and 48.1% (13/27) underwent at least two treatment protocols. In the remaining 55% (33/60) of calves that did not recover, 42.4% (14/33) had an ultrasonography score > 3 on the first evaluation, 72.7% (24/33) received at least two treatment protocols, and 93.9% (31/33) had at least three positive ultrasonographic examinations. Additionally, 29.3% of heifers (32/110) were treated and did not have positive evaluations on the ultrasonography examination closest to the day of treatment (Fig. 2).

Half of the treated animals showed improvement in lung condition by the 12th week of life. In the group of animals that did not recover, there was a higher proportion of severely affected animals on ultrasonography evaluation closest to the day of treatment (42.4% vs. 29.6%). Overall, 36% of the heifers had an ultrasonography score > 3 on the first treatment (Fig. 3).

Another point to be highlighted was the persistence of lung consolidation for at least six weeks in 93.9% (31/33) of the animals that did not recover and 44.44% (12/27) of those that recovered (Fig. 3).

Regarding passive immunity, the cutoff point for plasma protein to determine the failure of transfer of passive immunity (TP) used in this study was 5.8 g/dL (Elsohaby et al. 2019). Considering this, 2% (4/193) of the calves presented failure of TP, with a mean concentration of 7.5 g/dL (SD 0.84). Higher concentrations of plasma proteins showed a positive effect on respiratory health. For each increase of one point in plasma protein, starting at 5.0 g/dL, a significant association was observed in the reduction in the number of ultrasonographic consolidations > 1 cm in the GH ($y = 0.81-0.047$, $R^2 = 0.004$, $P = 0.021$) and TA ($y = 0.82-0.055x$, $R^2 = 0.0061$, $P = 0.003$) periods and in the number of cases treated for pneumonia until weaning ($y = 2-0.13x$; $R^2 = 0.021$; $P = 0.044$).

Assessment of the fecal score in the first 20 days of life showed that neonatal diarrhea affected 97% (188/193) of calves. Of the total cases, severe diarrhea affected 3.9% (7/188) of the calves, moderate diarrhea affected 61.7% (116/188), and mild diarrhea affected 34.5% (65/188). A significant effect was observed between the total number of diarrhea days and the number of cases treated for pneumonia ($y = 0.79+0.04x$; $R^2 = 0.022$; $P = 0.04$) during the pre-weaned period, but not the number of intercostal spaces with consolidations > 1 cm ($P > 0.05$). The average duration of diarrhea was 4.1 days (SD 1.1 days), and in calves with severe diarrhea, the average duration was 1.1 days (SD 2.3 days).

DISCUSSION

Relationship between respiratory disease, weight gain, first conception, and mortality

Animals that tested positive for respiratory disease based on thoracic ultrasonography were associated with lower weight gain, indicating a negative effect of respiratory disease on animal performance. This effect has been reported by other authors using the number of respiratory disease treatments performed by farmers (Donovan et al. 1998), standardized clinical examinations in score systems (Stanton et al. 2012, Virtala et al. 1996), and ultrasonographic diagnoses (Cramer & Ollivett 2019) as evaluation criteria. However, unlike previous studies, this study showed a relationship between the severity of lung injury and weight gain, as the greater the number of intercostal spaces with lung consolidations observed on ultrasonography, the lower the weight gain. The number of intercostal spaces with lesions greater than 1 cm had a positive effect on the time to reach a weight of 370 kg ($R^2 = 0.12$; $P = 0.001$) (Fig. 1). Animals with lung lesions gained less weight in the first six months of life, and there

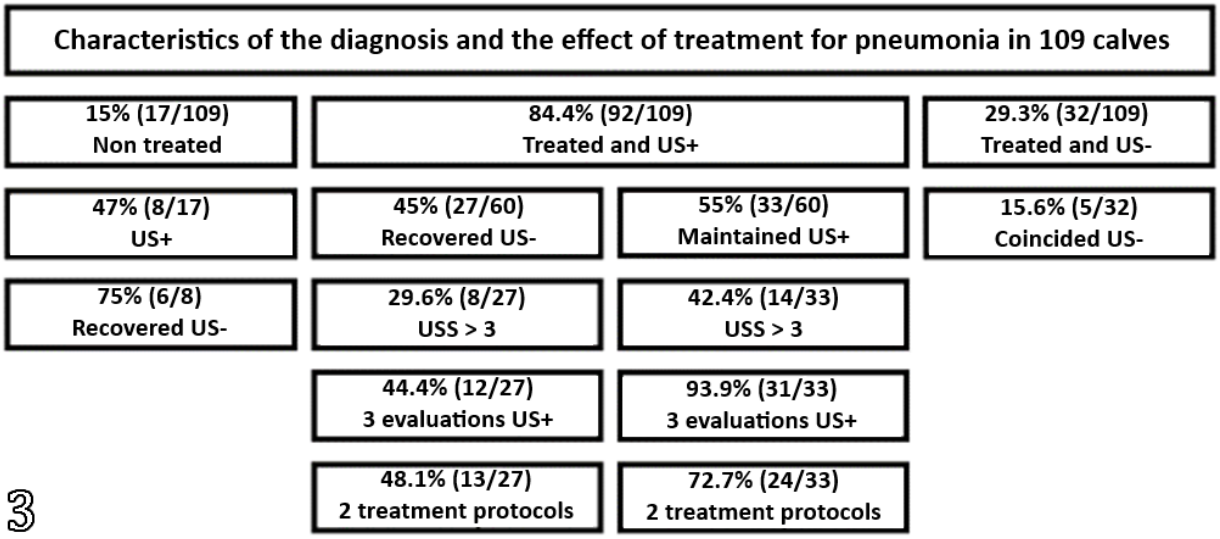

Fig. 3. Comparison of cases of untreated and treated animals for pneumonia, with the result of pulmonary ultrasonography examinations performed between the 4th and 12th weeks of life, of 109 Holstein heifers on an intensive dairy farm located in the Midwest of Brazil. US+ = positive thoracic ultrasonography examination; US- = negative thoracic ultrasonography examination; USS > 3 = sum of ultrasonography examinations with ultrasonography scores 4 and 5. Recovered US- presented a negative ultrasonography examination at the 12th week of life, and US+ maintained a positive ultrasonography examination.

was no compensatory gain later. This meant a greater chance of delaying the entry of these animals into reproduction.

Another point investigated by this study was the relationship between respiratory disease in the first six months of life and conception. However, no effect was detected on the average number of intercostal spaces with consolidations > 1 cm or the number of pneumonia cases during the pre-weaned period on the conception of the first pregnancy. This effect may not have been observed because of the standardization carried out by the farm with a minimum weight of 370 kg for entry into reproduction. At this point, the animals are similar and may have already recovered from the negative effects of the respiratory disease that occurred in the first months of life. In addition, severely affected animals may not survive until their first insemination. In contrast, a study that performed a single ultrasonography evaluation at two months of age on 613 Holstein heifers observed a lower pregnancy risk (HR = 0.7, 95% CI = 0.6-0.8; P = 0.006) in animals that presented with pulmonary consolidation > 1 cm (Teixeira et al. 2017). The difference between this result and what was observed in the present study is that these authors performed only one evaluation, and these animals may have had other moments with pulmonary consolidations over the six months of life, which were not evaluated.

The assessment of the relationship between the presence of lung lesions and mortality in post-weaning calves showed a direct association between them, with more severe lesions having a greater effect on mortality during the period. Other studies have found similar results but in a single evaluation (Teixeira et al. 2017, Dunn et al. 2018, Adams & Buczinski 2016). One of them observed that calves with lung consolidation in an ultrasonography examination performed at three months of age had a lower survival rate until one year of age. However, this association was only observed in animals with consolidations of ≥ 6 cm, evidence of abscess, or pleural effusion (Adams & Buczinski 2016). A second study found a higher risk of death in the first 350 days of life in animals with consolidation > 1 cm at weaning (Teixeira et al. 2017). A third evaluated calves weekly until two months of age and found that the presence of at least one case of lung consolidation > 3 cm during this period did not affect survival until the end of the first lactation (Dunn et al. 2018). Despite methodological differences in data collection and analysis, the presence of lung consolidation, as observed in this study, negatively affected the long-term survival of calves.

Number of pneumonia cases treated during the pre-weaning period and their relationship with thoracic ultrasonography, transfer of passive immunity, and days with diarrhea

The high incidence of cases treated for pneumonia in this study was related to the higher number of days with diarrhea in the first weeks of life and in animals with poor transfer of passive immunity. Other factors, although not measured, were present and may have contributed, especially ventilation conditions, high humidity, fecal accumulation, the use of waste milk, and heat stress.

In addition to the high number of treatments for pneumonia, 23.2% (45/193) of calves presented at least two cases, and 56.3% (80/142) received more than one antibiotic therapy protocol in the same case. These values were high, indicating the low efficiency of the treatment protocols used. One reason for this may be the duration of treatment, which guaranteed a maximum of four days of antibiotic coverage with two applications of amoxicillin and/or florfenicol every 48 hours. A review on the use of antimicrobials in the treatment of respiratory diseases found that there is no consensus on the ideal minimum period; however, most studies indicate better efficacy in protocols that guarantee seven days of antibiotic action (Apley 2015).

Additionally, the study design itself may have influenced the number of treatments for pneumonia since the presence of a case of lung consolidation identified on ultrasonography was reported to the employee responsible for the treatment, directly affecting their decision-making and leading to the treatment of animals that would not be evaluated in the employee's routine, as they were subclinical cases or presented discrete clinical signs. Similarly, another study observed that 80.5% of heifers were treated up to 60 days of age, and the majority received three antibiotic therapy protocols on two farms with a high challenge for respiratory disease. Furthermore, remission of lung lesions in animals that were never treated (6/109) demonstrated that spontaneous recovery of pulmonary consolidation can occur, although few cases were observed in this study (Binversie et al. 2020). These findings were corroborated by a review that compared randomized clinical trials and reported that a cure for respiratory diseases does not always occur because of the administration of antibiotics. In some cases, a competent immune system is expected to respond successfully to certain infections (Dedonder & Apley 2015).

Another point to be highlighted was the persistence of pulmonary consolidation for at least six weeks, both in animals that did not recover and in those that did. This shows that lung lesions were present for long periods, even in animals that were successfully treated. This may be related to antimicrobial resistance to the drugs used, the duration of the treatment implemented, late initial diagnosis, low immune response capacity of the animals, and lack of supportive therapy. However, the ideal time for recovery from pulmonary consolidation after a pneumonia episode requires further study.

Finally, the presence of treated calves that did not show positive evaluations on ultrasonography examination near the day of treatment (32/110) may be related to pneumonia diagnosis errors on the farm. More precisely, this may be because treatments were performed in the interval between collections, treatment of animals with upper respiratory tract disease, or even error in the interpretation of clinical signs by the employee.

The variation in the occurrence of treatments over time (Fig. 2) can be explained by several factors. Among them, diarrhea, which affects calves mainly from the second week of life, stands out. Although diarrhea increased the number of cases treated for pneumonia, the observed effect was low (R^2 = 0.022). Diarrhea can predispose to respiratory disease by eliciting an inflammatory response and causing systemic metabolic disturbances such as dehydration, hypoglycemia, acid-base and electrolyte disorders, which directly affect the full capacity of the immune system's defenses and impair the respiratory ciliated epithelium function (Ackermann et al. 2010). The inflammatory response requires energy expenditure to produce inflammatory mediators; simultaneously, inflammatory conditions can lead to depression and reduced

food intake (Bordera et al. 2008, Gorden & Plummer 2010). Dehydration increases the viscosity of respiratory secretions and diminishes the periciliary liquid layer, compromising the proper beating of cilia and impairing the clearance system of the respiratory tract (Ackermann et al. 2010). Cellular functions depend on energy and a range of biochemical and enzymatic reactions that operate optimally within a specific pH range. In the group of animals evaluated, the diarrhea period was short, with an average of 4.1 days (SD 1.1 days). In the few calves that had severe diarrhea, the average duration was 1.1 days (SD 2.3 days). This may have reduced the immunosuppressive effect and explained the discrete effect in its relationship with respiratory disease. In addition, most animals had diarrhea for similar periods, which limited the analysis of their relationship with respiratory disease.

Another factor that must be considered is the decrease in passive immunity, which has a protective immunological effect for two to four weeks of life (Chase et al. 2008, Hulbert & Moisá 2016). After this period, the animal goes through a moment of greater susceptibility to infections, called the "window of susceptibility," when the protection of passive immunity is transferred by colostrum ingestion drops, and the animal is still developing an effective acquired immune response (Hulbert & Moisá 2016). This study demonstrated that an effective transfer of passive immunity is responsible for better lung health, and the better the passive immunity, the greater its effect on the extent of lung consolidation and the number of cases that required treatment for pneumonia.

Despite the positive relationship between improved immune transfer efficiency and respiratory health, this effect was very low ($R^2 = 0.0061$ and $R^2 = 0.021$, respectively). This is likely related to the multifactorial nature of respiratory diseases, and a single isolated factor would hardly be responsible for explaining its occurrence in its entirety. Additionally, a high concentration of plasma protein was observed in the evaluated group of calves (mean 7.5 g/dL, SD 0.84), and 98% showed adequate passive immune transfer, which limited the ability to predict more significant differences in relation to respiratory disease.

Other studies have also observed a protective effect of good colostrum intake on respiratory diseases. A study that followed 2,874 calves found that serum protein levels < 5.7 g/dL in the first week of life resulted in a two-fold increase in the risk of respiratory disease up to five weeks of age (Windeyer et al. 2014). A second study evaluating serum IgG concentration in the first two weeks of life found that lower values doubled the chance of developing respiratory disease (Virtala et al. 1999).

The important finding of the present study was that the increase in plasma protein concentration represented less lung injury, characterized by a reduction in the number of lung consolidations of > 1 cm. This result, although modest, demonstrates a direct relationship between passive immune transfer and lung health. Ultrasound, compared to respiratory scores, allowed for the identification of actual lung injury and better association with the severity of the process by inferring the affected lung area with consolidations. Thus, these results are more consistent than those from previously published studies that assessed this relationship through the diagnosis of respiratory disease based on physical examination and farm treatment records (Virtala et al. 1996, Windeyer et al. 2014, Pardon et al. 2019). These are subjective diagnostic methods that are incapable of accurately determining whether an animal has a respiratory disease and if it is related to pneumonia. Recently, one study investigated this effect using thoracic ultrasound but found no association between a total serum protein cutoff of 5.2 g/dL and the presence of lung consolidation (Dunn et al. 2018).

CONCLUSIONS

Our study reinforces the value of thoracic ultrasonography in the characterization and quantification of respiratory diseases in cattle. Respiratory disease is multifactorial in nature, and in this study, its frequency was discretely related to a worsening of passive immunity transfer efficiency and an increase in the number of days of diarrhea.

The extension of lung consolidation has a proportional and negative effect on weight gain for up to six months with no compensatory gain later. Additionally, the mortality rate increased by an average of 51% for each unit above the mean value of the number of intercostal spaces with consolidations > 1 cm.

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Data availability statement.- The data used in this study are available and can be accessed upon request from the corresponding author.

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