Evaluation of White Blood Cell, Fibrinogen, Serum Amyloid A, and Ultrasonographic Grade to Refine a *R. equi* Screening Program

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Thoracic ultrasound screening program incorporating white blood cell (WBC) and/or serum amyloid A (SAA) in conjunction with grade and use of grade size alone (initial and maximum) may reduce overtreatment of subclinical animals without significantly increasing the risk of clinical *R. equi* pneumonia. Author's address: Hagyard Equine Medical Institute, 4250 Iron Works Pike, Lexington, KY 40511; e-mail: jmccracken@hagyard.com.

1. Introduction

Rhodococcus equi pneumonia in foals is an important disease in the equine industry. Clinical cases often have devastating results, due to the severity of disease and corresponding economic impact of prolonged treatment, management changes and possible loss of life. Foals are infected within the first few days or weeks of life.[1,2] The organism is fairly ubiquitous and disease progression is insidious, with clinical respiratory disease appearing typically between 4 weeks and 3 months.[3] *R. equi* pneumonia is hallmarked by pyogranulomatous lung lesions, and clinically manifests with marked elevation of body temperature, coughing, and/or increased respiratory rate and effort. Significant elevations in white blood cell (WBC) count and fibrinogen level are typical laboratory findings with clinical disease.

Identifying a way to detect and address *R. equi* pneumonia prior to clinical disease has been the focus of much research. Laboratory testing has proven to be unrewarding when used alone as an early detection method. It has been shown that use of ELISAs, agar gel immunodiffusion (AGID) and a synergistic hemolysis inhibition assay are inadequate for early detection of *R. equi* pneumonia.[4,5] PCR to identify the presence of virulent *R. equi* in feces is quite sensitive and specific in clinically ill foals,[6] but its use in predicting subclinical or eventual clinical animals has proved unrewarding.[7] The use of WBC counts has been shown to be more beneficial than fibrinogen concentrations in early detection of clinical *R. equi* pneumonia,[5] however, lacks specificity. An elevated WBC alone is useful only as an indicator for further investigation into the source of inflammation. While WBCs seem to be more helpful than fibrinogen, serial fibrinogen levels may be more helpful than serum amyloid A (SAA) levels.[8] A study showed serial fibrinogen rises in relation to foal age may predict subclinical *R. equi*, but again lacks specificity and has not been applied to development of clinical disease. SAA has been inadequate as a predictive tool,[8,9] and in fact one study showed SAA was negative in 28% of clinical *R. equi* pneumonia cases.[9]

NOTES

The use of thoracic ultrasound to identify subclinical *R. equi* pulmonary infection with subsequent various antibiotic therapies has been honed into a very successful screening method to prevent clinical *Rhodococcus* pneumonia.[3,10] This program has greatly reduced incidence of clinical cases of *R. equi* pneumonia and has accordingly become widespread practice. However, endemic properties may have a staggering prevalence of subclinical infection (presence of ultrasonographic lung lesions without clinical signs of illness) within their foal crop.[3,10] Although many juvenile animals develop subclinical disease, a much smaller percentage actually develops clinical respiratory disease. Recent studies have confirmed that the majority (79%[11] and 88%[12]) of subclinical individuals resolve lesions without any signs of clinical disease. The reason that some foals (Regressors) are able to resolve these lesions without ever becoming ill, while others (Progressors) eventually develop clinical disease eludes veterinarians at this time. Unfortunately, which category a subclinical foal will eventually fall into is also currently unable to be predicted.

The inability to foresee the outcome of a foal with subclinical thoracic lesions has commonly resulted in treatment of all or the majority of subclinical animals. This use of antimicrobials not only results in a high percentage of foals receiving antibiotics that have potential detrimental side effects, but may also be contributing to the development of antibiotic resistant strains of *R. equi*. There has been one published report of a macrolide-resistant strain documented on a farm that had been screening and treating for 7 years.[13] Laboratory data indicates that resistance to one macrolide infers resistance to all. With resistant strains clearly appearing, it has become imperative to be able to determine which foals are Regressors versus Progressors. The questionable benefit of treating such a high percentage of foals is further compounded by a study which indicated that the length of time from lesion discovery to resolution is not shortened by antimicrobial treatment.[14]

Advancement of thoracic screening programs is needed, specifically a way to predict the outcome of subclinical animals in a manner applicable for field practitioners. Establishing a system to more accurately identify animals at risk of clinical disease would greatly reduce overtreatment, allowing continued disease prevention while curbing practices leading to antimicrobial resistance. The incorporation of laboratory testing into thoracic ultrasound screening may potentially refine the system. The ability of WBCs, SAA, and fibrinogen in conjunction with thoracic ultrasound to predict subclinical case outcome was investigated.

2. Materials and Methods

Ninety-six Thoroughbred foals on an endemic *R. equi* farm in central Kentucky were enrolled in the study in spring 2016. The property had utilized thoracic screening as a preventative practice since 2004. In 2004 and 2005, transtracheal aspirates were performed on the first five individuals identified with subclinical lesions. Cultures of the aspirates confirmed *R. equi* as the causative agent. From 2006 to date foals were considered to have subclinical *R. equi* if lesions typical of *R. equi* were identified on thoracic scan at the appropriate age.

Thoracic Ultrasounds

Foals were scanned on a schedule of 4, 6, and 8 weeks of age. Once thoracic ultrasound lesions were identified, foals began weekly evaluations until lesion(s) resolution. Measurements (x- and y-axis) and location were recorded for every lesion visualized, and each lesion was assigned a grade following the Slovis grading system[10] based on its largest diameter. Foals were then assigned a grade for that point in time corresponding to the single largest grade of lesion present. Foals were not treated with antibiotics unless clinical evidence of respiratory disease was noted or exclusion criteria were met. Each animal was categorized retrospectively as a Progressor, Regressor, or Excluded. For each foal, data was sorted by grade assigned at the initial positive scan, maximum grade attained, and eventual classification of the foal.

Blood Sampling/Testing

Blood was collected from the jugular vein of every foal immediately following every scan that visualized a lesion. Samples were run on the day of the exam for WBC count and fibrinogen levels. Serum for SAA levels was frozen and banked until the completion of the study. Each blood sample was categorized by the grade assigned to the foal at the time of collection. Samples were also classified by the category to which the foal was retrospectively assigned. No blood samples were included on any foals after removal from the study; accordingly, no results reflect the influence of any antimicrobial therapy.

Rectal Temperature

Once identified as subclinical, rectal temperatures were recorded twice daily for each foal.

Clinical Disease Criteria

The presence of fever $>102.5°F$, significant coughing, and/or increased respiratory effort was considered evidence of clinical *R. equi* pneumonia. For all foals thus classified, full physical examinations were performed to ensure that the symptoms were correctly associated with *R. equi* pneumonia rather than other maladies of young foals. Once identified as clinical, foals were removed from the study and started on medical therapy.

Exclusion Criteria

The exclusion criteria consisted of a lesion ≥ 5.0 cm diameter (grade 6+), WBC $\geq 18{,}000$ cells/μL, and/or

Table 1. Analysis of Laboratory Results by Clinical Outcome (Progressor Versus Regressor)

	WBC			SAA			Fibrinogen		
	Avg (K/μL)			Avg (μg/mL)			Avg (mg/dL)		
	Pro	Reg	*P*-value	Pro	Reg	*P*-value	Pro	Reg	*P*-value
All Grades	14.8	11.5	.000139	718	49	1.66E-08	425	358	.129006
Grade 5	16.2	13.6	.052547	1282	52	.029345	500	417	.776398
Grade 4	14.1	11.5	.154139	106	118	.96054	350	404	.642494
Grade 3	16.4	11.3	.060962	29	39	.941618	400	367	.79252
Grade 2	12.4	11.3	.597342	229	8	.000612	333	303	.727691

Avg, average; Pro, progressor; Reg, regressor.
The table shows *P*-values for differentiating between Progressors and Regressors using WBCs, SAA, fibrinogen, and lesion grades, where $P < .05$ is considered statistically significant (highlighted).

fibrinogen ≥ 800 mg/dL. If a foal met any one or more of these parameters, it was removed from the study and medical therapy initiated. Any foal that was found to have other sources of inflammation at the time of blood sampling was also removed from the study.

Inclusion Criteria

The inclusion criteria consisted of a lack of clinical evidence of respiratory disease, positive ultrasound scans with a lesion(s) < 5 cm diameter (grade 5 or below), WBC < 18,000 cells/ μL, and/or fibrinogen < 800 mg/dL.

Statistical Analysis

Data were organized and analyzed in a manner that would be of practical use when implementing a screening program in practice. In order to determine the ability of WBCs, SAA and fibrinogen in conjunction with thoracic ultrasound to predict subclinical case outcome, correlations of lesion grade sizes and laboratory results (WBCs, SAA, and fibrinogen) and correlations of clinical outcome (Progressor versus Regressor) and laboratory results (WBCs, SAA and fibrinogen) were analyzed using single-factor ANOVAs. Fisher's Exact test was used to compare likelihood of clinical disease development between groupings of ultrasound grades. Descriptive statistics were used to evaluate each laboratory test at different grade cutoffs to establish a grade + lab result level (WBCs, SAA, and fibrinogen), which would allow practitioners to better differentiate between Regressors and Progressors.

3. Results

Of the 96 foals in the study, 54 foals were identified as having subclinical lesions by thoracic ultrasound examination. Twelve individuals met exclusion criteria and were not included in data analysis. The foals that were excluded from the study were removed for elevated WBCs (6 foals), lesion ≥ 5.0 cm diameter (3 foals), both elevated WBC and large lesions at the same exam (1 foal), and extenuating circumstances (2 foals). No foals were removed due to elevated fibrinogen levels. The remaining 42 foals were evaluated weekly until clinical disease developed (7 Progressors) or lesions resolved (35 Regressors). The percentage of spontaneous resolution in this study was 83% (35/42). Clinical disease was first noted in the Progressors at grade 5 (4 foals), grade 4 (1 foal), grade 3 (1 foal) and grade 2 (1 foal). All Progressors developed clinical disease within seven days of initial identification of subclinical disease. Data collected from excluded animals was not analyzed, therefore it is important to note that no information regarding grade 6 or higher is contained in the following results.

Correlation of WBC, Fibrinogen, and SAA to Ultrasound Grade and Foal Category

Statistically significant variation existed in WBC counts and SAA levels between Progressors and Regressors, but not fibrinogen levels. Statistical differences between Progressors and Regressors within each grade were also looked at with single-factor ANOVAs and did not prove significant for any of the three laboratory tests at any grades except SAA at grade 5 and SAA at grade 2 (Table 1). There was a correlation with grade for all three laboratory tests (WBC, SAA, and fibrinogen) (Table 2).

Use of Ultrasound Alone to Predict Outcome of Subclinical Animals

The initial grade assigned each foal was evaluated for likelihood of clinical disease development compared with smaller initial grades. In this study, foals with an initial grade 5 were more likely to develop clinical disease than foals with initial grades less than 5. There was no statistical difference in likelihood of progression to clinical disease between foals with initial grades 4+5 compared with foals of lesser initial grades (Fig. 1). Similar analysis was performed on the maximum grade attained for each foal. Individuals that reached a grade 5 were more likely to develop clinical disease than foals that did not develop lesions of that magnitude, while no statistical difference existed using a smaller grade cutoff (Fig. 2).

In this study, early identification of clinical disease by thoracic ultrasound alone had perfect sensi-

Table 2. Analysis of Laboratory Results by Grade Using Single-Factor ANOVAs Where *P* < .05 is Considered Statistically Significant (Highlighted)

	WBC Average (K/μL)	SAA Average (μg/mL)	Fibrinogen Average (mg/dL)
Grade 5	15.1	636	469
Grade 4	12.5	249	429
Grade 3	12.0	50	369
Grade 2	11.5	33	312
Grade 1	12.9	1	267
P-Value Between Grades	.014193	.000709	.000997

SSA, serum amyloid A; WBC, white blood cell.

tivity, but an average specificity and a very poor positive predictive value (PPV). Using the mere presence of a thoracic lesion (all grades other than grade 0) to predict the outcome of subclinical animals had the same perfect sensitivity and very poor PPV but totally lacked specificity (0%) (Table 3).

A cutoff of grade 5 (both as initial grade and maximum grade) yielded marked improvement over general ultrasound identification in specificity and PPV; however, there was a huge decrease in sensitivity for predicting the development of clinical disease. By using a smaller grade as a cutoff (grades 4+5) sensitivity was mildly improved to the detriment of specificity and PPV (Table 3).

Use of Laboratory Results in Conjunction with Ultrasound Grade to Predict Outcome of Subclinical Animals

When evaluated across all ultrasound grades, elevation in WBC count was unable to provide perfect sensitivity but did improve PPV compared with ultrasound alone. At a level of 13.5 K/μL or higher (normal, 5.0–12.0 K/μL), WBCs across all grades delivered a fair sensitivity and a mildly improved PPV. Mild elevation in WBCs when a foal was a grade 3 or higher (grades 3+4+5) at the time of sampling would have been a successful predictor of clinical outcome in this study (Fig. 3). A WBC cutoff of 13.5 K/μL provided perfect sensitivity and an improved, but still fairly poor, PPV. Raising the cutoff value to 14.0 K/μL sacrificed sensitivity with marginal improvement in PPV. Limiting WBC sampling to foals with grades 4+5 had similar sensitivity at the same limits and significant improvement of PPV (Table 3).

Similar to the predictive capability of WBC counts in this study, mild elevation in SAA level (≥75 μg/mL; normal, <3 μg/mL) across all ultrasound grades was also unable to provide perfect sensitivity but did yield a stronger PPV than with that of ultrasound alone. In the study population, correct prediction of the clinical outcome of subclinical animals was possible using the same SAA level when the ultrasound grade was a 4 or higher (grades 4+5) (Fig. 4). A strong PPV was also evident with this combination. Extending the range to include foals with

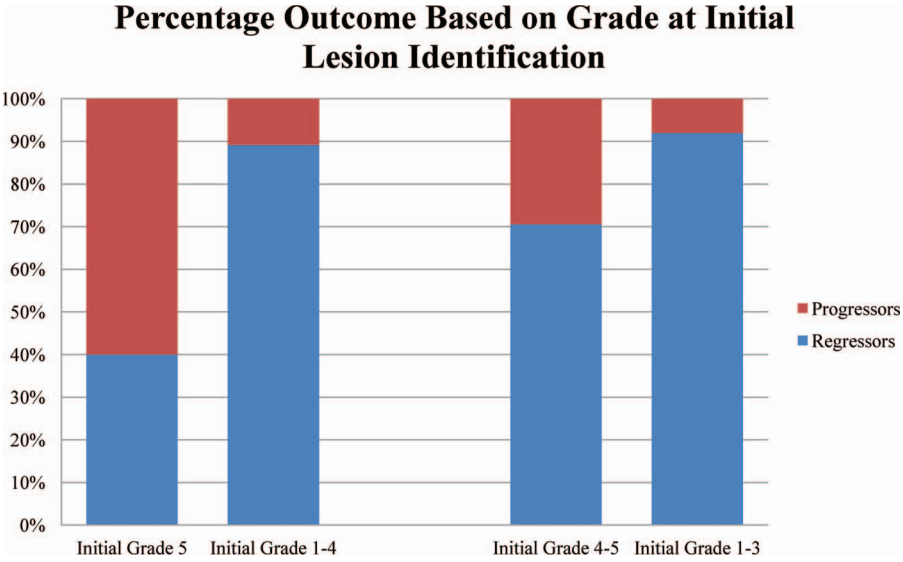

Fig. 1. Percentage of foal outcome based on grade at initial lesion identification, where Progressors are represented by red and Regressors are represented by blue. Fisher's Exact Test ($\alpha = 0.05$) showed statistical difference between Initial Grade 5 and Initial Grades <5 ($P = .025945$). The same test showed no statistical difference between Initial Grades 4+5 and Initial Grades <4 ($P = .098818$).

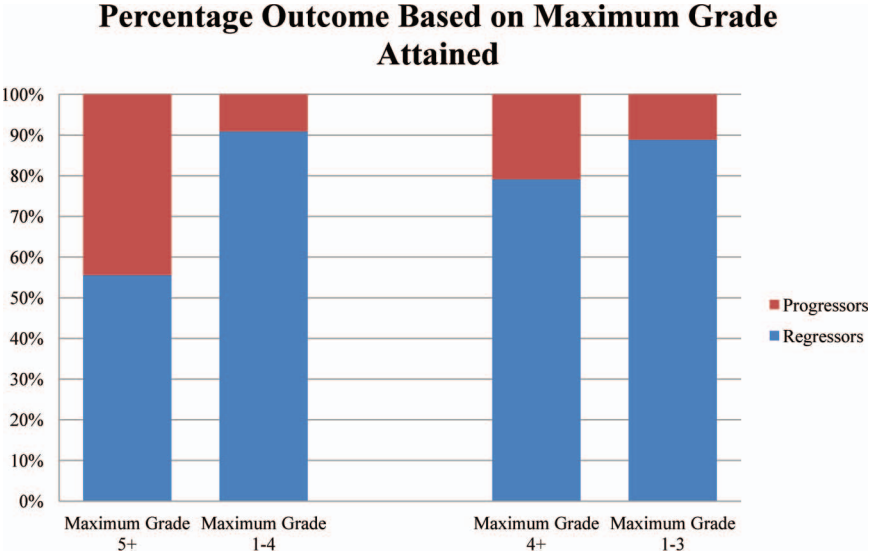

Fig. 2. Percentage of foal outcome based on maximum grade attained, where Progressors are represented by red and Regressors are represented by blue. Fisher's Exact Test ($\alpha = 0.05$) showed statistical difference between Maximum Grade 5 and Maximum Grades <5 ($P = .028052$). The same test showed no statistical difference between Maximum Grades 4+5 and Maximum Grades <4 ($P = .678601$).

grade 3 was unable to maintain perfect sensitivity but still had a solid PPV (Table 3).

The combination of all ultrasound grades with elevated fibrinogen levels (normal, 200–500 mg/dL) was extremely poor at predicting the progression to clinical disease (Fig. 5) with an extremely low sensitivity and a low PPV. Even when limited to just grade-5 animals, elevated fibrinogen (≥600 mg/dL) generated very poor sensitivity (Table 3).

4. Discussion

Use of thoracic screening with treatment of all or almost all lesions has greatly reduced clinical *R. equi* pneumonia; however, has resulted in significant overtreatment. During the 12 years prior to

Table 3. Descriptive Statistics Using Ultrasound Grading, WBCs, SAA, and Fibrinogen to Identify Progressors vs Regressors, Where Progressors Are Considered the Diseased Group and Regressors Are Considered the Nondiseased Group

	Sensitivity	Specificity	PPV	NPV
Clinical Identification				
Ultrasound—All Grades (1–5)	100	54	17	100
Subclinical Outcome (Progressor v Regressor)				
Ultrasound—All Grades (1–5)	100	0	17	n/a
Initial Grade 5	43	94	60	89
Initial Grade 4–5	71	66	29	92
Maximum Grade 5	57	86	44	91
Maximum Grade 4–5	71	46	21	89
U/S All Grades (1–5) + WBC ≥13.5 K/μL	83	74	27	97
U/S Grades 3–5 + WBC ≥13.5 K/μl	100	75	33	100
U/S Grades 3–5 + WBC ≥14.0 K/μl	89	80	36	98
U/S Grades 4–5 + WBC ≥13.5 K/μl	100	69	44	100
U/S Grades 4–5 + WBC ≥14.0 K/μl	88	78	50	96
U/S All Grades (1–5) + SAA ≥75 μg/mL	75	91	50	97
U/S Grades 3–5 + SAA ≥75 μg/mL	89	87	47	98
U/S Grades 4–5 + SAA ≥75 μg/mL	100	81	57	100
U/S Grades 4–5 + SAA ≥100 μg/mL	88	84	58	96
U/S All Grades (1–5) + Fibrinogen ≥600 mg/dL	25	89	21	91
U/S Grade 5 + Fibrinogen ≥600 mg/dL	50	83	75	63

NPV, negative predictive value; PPV, positive predictive value; SSA, serum amyloid A; WBC, white blood cell.

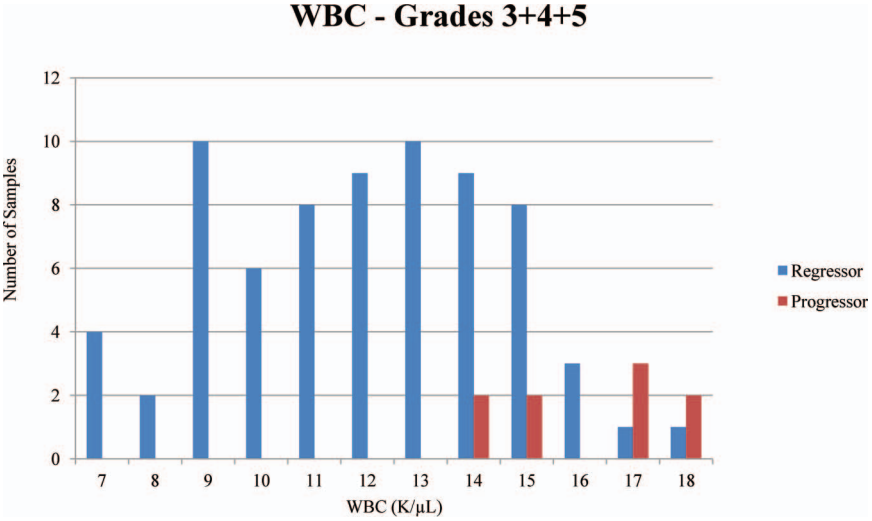

Fig. 3. A histogram of WBC counts of Regressors (blue) and Progressors (red) at ultrasonographic grades 3+4+5, where the x-axis shows WBC levels and the y-axis shows the number of patients affected.

this study, treatment protocol on the study property typically involved antibiotic treatment of foals with grade 2 lesions and larger. Clinical *R. equi* pneumonia had been all but eliminated on the property. Assuming the study year would have followed the patterns of the previous 12 years, 55 animals would have been treated with no clinical pneumonia cases if the established protocol had been continued. With participation in this study, only 19 animals were treated; 7 foals once they developed clinical disease and 12 once they met exclusion criteria. The disparity between treatment group numbers exhibits the flaw of the established thoracic screening program.

Clients and veterinarians most likely initiate *R. equi* prevention programs largely in response to significant clinical disease experienced historically. This may have been due to high morbidity rates and associated length of treatments, management changes, and intensity of labor involved with clinical cases in a previous year or it may have involved one or more significant (economic and/or emotional) mortality. It is assumed that continuation of a thoracic screening program reflects client and veteri-

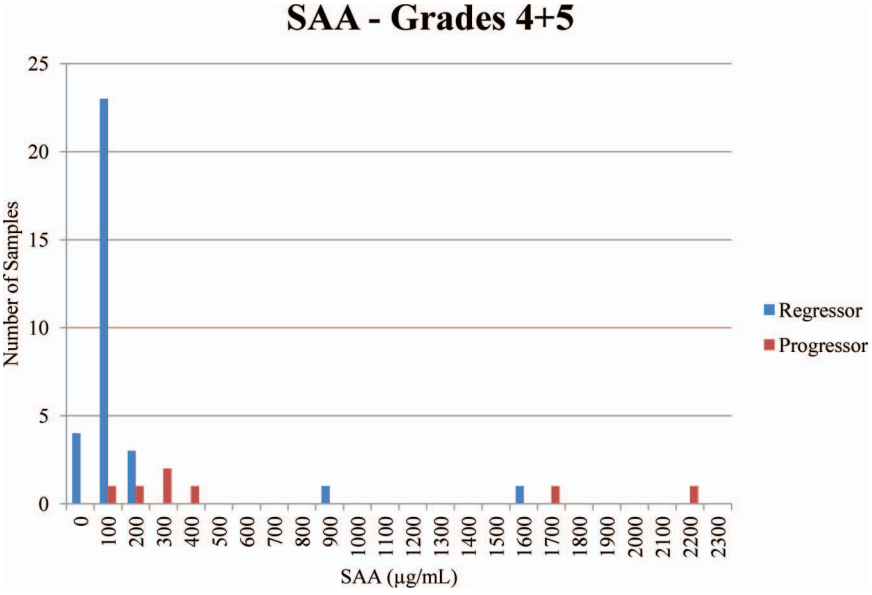

Fig. 4. A histogram representation of SAA levels of Regressors (blue) and Progressors (red) at ultrasonographic grades 4+5, where the x-axis shows SAA levels and the y-axis show the number of patients affected.

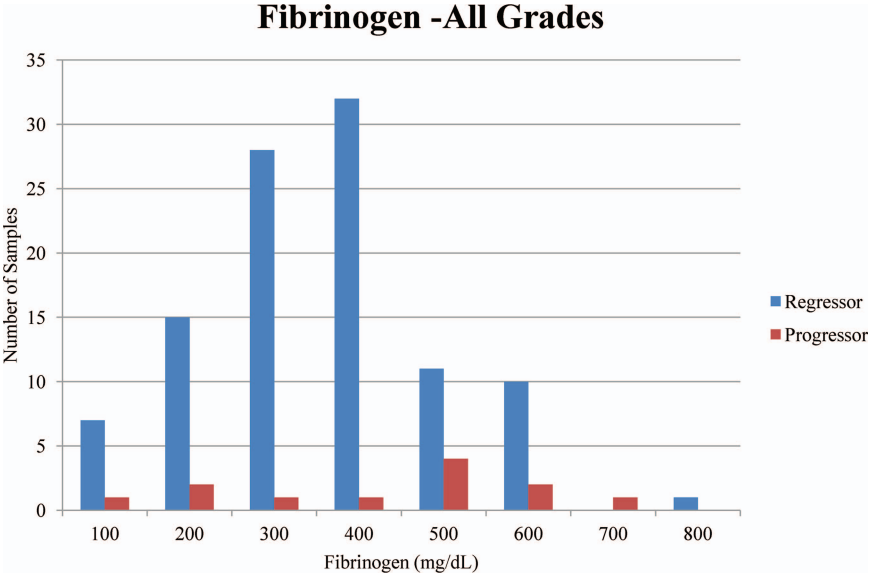

Fig. 5. A histogram representation of fibrinogen concentration of Regressors (blue) and Progressors (red) across all ultrasonographic grades, where the x-axis shows fibrinogen levels and the y-axis shows the number of patients affected.

narian satisfaction with the program's ability to decrease the incidence of clinical cases. Although clients may not be enamored with the expense of the screening, costs and side-effects of antibiotic therapy, management changes due to treatment protocols and ethical repercussion of overtreating, many are justifiably reluctant to make program changes that could increase the risk of clinical disease. After reaching a satisfactory level of clinical disease on an endemic property, it is also difficult for veterinarians to recommend changes to an established screening program that may increase the risk to individuals.

The goal of this study was to expand the approach of screening programs to improve veterinarians' ability to predict which individuals would develop clinical *R. equi* pneumonia. The rate of spontaneous resolution in this study and those previously published are very similar.[11,12] These values correlate with the PPV of ultrasound (all grades). Practical interpretation of the PPV is the percentage of those being identified that would have become clinically ill. The PPV of ultrasound (all grades) is 17% in this study. A higher PPV would result in treatment of fewer Regressors.

While an improvement in PPV is much desired for screening programs, it should not be accepted at a significant loss of sensitivity. In the study population, thoracic ultrasound correctly identified all seven individuals that progressed to clinical disease. Sensitivity of thoracic ultrasound (all grades) is the percentage of animals that were going to develop clinical disease that were identified, 100% in this study. In fact, thoracic ultrasound (all grades) had a perfect sensitivity for each of the previous 12 years on the study property.

In this study, the PPV generated by using bloodwork (WBC, SAA, or fibrinogen) with all thoracic ultrasound lesions (all grades) was an improvement over that of ultrasound alone (Table 3); however, sensitivities correlating to each lab test in conjunction with all grades were less than perfect. While fibrinogen did not prove to be helpful at all in the prediction of progression to clinical disease, WBC and SAA appear to be of substantial assistance especially when applied to higher grade foals. Sensitivity of 100% was able to be achieved when WBC and SAA were evaluated at the point of larger thoracic grades. The combination of WBC with grades 3+4+5 and SAA with grades 4+5 both were able to maintain 100% sensitivity while improving PPV over that of ultrasound (all grades). Although the improvements in PPV compared to ultrasound alone were not extreme, they are nonetheless significant. Decreasing unnecessary treatment by even a few animals would be beneficial. In this study, using higher cutoff values for the laboratory results did improve the PPVs even more; however, doing so sacrificed the perfect sensitivity (Table 3).

Comparing the descriptive values of WBCs and SAA in this study, perfect sensitivity was able to be achieved for a larger population of foals (grades 3+4+5) when using WBCs with ultrasound than with SAA and ultrasound (grades 4+5). Although SAA had a stronger PPV at grades 4+5 than that of WBC at the same grades, the ability to successfully apply WBC cutoffs to more foals at an additional grade is significant in practice.

Ideally, a lab test would have been identified that could have been used reliably at all grade levels. In addition to evaluating the lab values of Progressors versus Regressors in light of a grade cutoff, all

three tests were examined between the two groups at each individual grade level (Table 1). A loose variance between WBCs of Progressors and Regressors was evident for all but grade 2. Only three samples for Progressors were taken at grade 2. One result (WBC, 13.7 K/μL) was the initial sample from a foal whose lesion grew in size in a week. The foal became clinical after the second exam, at which point its WBC was 16.4 K/μL while a grade 3. Both blood results would be predictive using the 13.5-K/μL cutoff. The other two grade-2 Progressor samples were from the single foal that became clinical while only a grade 2. This foal had a WBC count of 12.4 K/μL at the initial grade 2 and subsequently 11.0 K/μL at the time of fever (103.4°F) 2 days later. All the other six Progressors had a rise in WBC count at the point of fever, suggesting that this individual may have been an incorrect inclusion as clinical *R. equi* pneumonia. Removing this animal from the study, the use of a WBC count cutoff of 13.5 K/μL would have yielded a perfect sensitivity across all grades.

Although initial and maximum grade had poor sensitivity for determining the likelihood for clinical disease, they had comparably powerful PPVs, especially initial grade 5. In the study, the exclusion criteria included presence of a grade 6 lesion or larger. Accordingly, no inference can be made about the behavior of subclinical lesions of this magnitude. However, some practitioners may be swayed by the likelihood of a grade 5 lesion becoming clinical being significantly more than that of lesser grades. Perhaps refinement of a screening program could include grade 5+ as a parameter for treatment, which would lower the PPV of the program but perhaps improve comfort level for clients accustomed to treating all lesions.

Seven animals developed clinical disease during the course of this study. All seven cases responded very quickly to antimicrobial treatment such that fevers were limited to three or fewer days for each individual. No foals required hospitalization, climate control, or supportive oxygen therapy. Although all the clinical cases in this study would be considered mild examples of *R. equi* pneumonia, the small sample size begs caution in making a broad assumption minimizing the potential seriousness of postponing treatment of a subclinical animal. Delaying treatment onset could well result in extremely severe respiratory disease requiring intensive care and may result in patient death.

If an established thoracic screening program were to incorporate WBCs and/or SAAs to decrease treatment of subclinical animals, it would be vital for veterinarians and clients to fully discuss and agree on the potential trade of sensitivity strength for improved PPV. It is up to the discretion of all those involved to decide what cutoff levels would provide enough confidence in risk of disease development balanced with the desire to treat more discriminately. If circumstances dictate, comfort level may be evaluated and limits set for each individual animal rather than for the foal crop as a whole, based on the economic and emotional value of particular animals. Other properties may decide to take more risk and raise treatment criteria levels or laboratory cutoff levels. It is also of vital importance that lab variation be taken into account when establishing a cutoff level for a particular property. The values and statistical numbers produced by this study are the result of one property, one season, and one laboratory. Results will vary across laboratories and cutoff levels for other labs cannot be accurately inferred or extrapolated from this study.

Although the subclinical incidence and grade breakdown of the study population was similar to that of the property over each of the past 12 years, 1 year of data does not have extreme strength. It is hoped that cautious adoption of the union of WBC and SAA with ultrasound grade will be beneficial to thoracic screening programs already established. It is also hoped that practitioners will continue to advance this method of refinement and share results for further improvement of the prevention of clinical *R. equi* pneumonia.

Acknowledgments

Declaration of Ethics

The Author has adhered to the Principles of Veterinary Medical Ethics of the AVMA.

Conflict of Interest

The Author has no conflicts of interest.

Antimicrobial Stewardship Policy

The aim of this study was to evaluate disease progression and corresponding laboratory and ultrasound results without therapeutic intervention, as such no animals received antimicrobials while actively participating in the study. If an animal became clinical or met exclusion parameters, the animal was removed from the study prior to initiation of antimicrobial therapy.

Funding Source

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