5. Discussion:

5.1 Discussion of section one: The clinical and prognostic significance of radiographic pattern, distribution and severity of thoracic radiographic changes in neonatal foals

5.1.1 The equine neonatal radiographic scoring system

Thoracic radiography is potentially a sensitive and specific imaging technique for the investigation of equine neonatal respiratory disease (Toal and Cudd 1987). The radiographic evaluation is facilitated by classifying the image appearance into radiographic patterns of pulmonary disease (interstitial, bronchial and alveolar pattern, Table 5) (Myer 1980). A numeric chest radiograph score further allows easy comparison between radiographs and decreases the degree of subjective variability of interpretation. However, the scoring system must be consistent within and between observers, and must have sufficient range and sensitivity to differentiate between degrees of disease severity (Conway SP 1994). The correlation between radiographic and clinical disease severity remains poorly described (Toal and Cudd 1987), although an extensive alveolar pattern generally indicates a severe respiratory disorder (atelectasis, respiratory distress syndrome, pneumonia etc.) (Toal and Cudd 1987; Lester and Lester 2001), while the interstitial pattern commonly pertains to an earlier or milder form of disease. In order to limit overestimation of radiographic disease severity, a higher radiographic score-range was assigned to the alveolar pattern, relative to other pattern scores. Therefore, foals with an extensive alveolar pattern automatically obtained the highest regional radiographic score, unrelated to any additional presence of interstitial or bronchial disease (Figure 3). Similar weighted chest radiograph scoring systems have also been developed for humans (Maconochie, Greenough et al. 1991).

An "assessment" score was also used to describe the general severity of pulmonary infiltrates, as viewed by each individual interpreter in the study. This "assessment" score was significantly correlated with the corrected total score of our radiographic scoring system (R =

0.9, $p<0.0001$). All interpreters had extensive experience in the interpretation of neonatal thoracic radiographs, which decreased the inconsistency and variability of a subjective evaluation. For people with limited exposure to radiographic interpretation and those less familiar with the guidelines of pattern recognition, the radiographic scoring system may aid in the prognostic and more objective interpretation of thoracic images. Additionally, a numeric interpretation of radiographic changes was essential in this study, in order to selectively explore the relationship between radiographic pattern and distribution, and clinical variables in neonatal foals.

Nonetheless, both the "assessment" score and radiographic scoring system are based on a subjective interpretation. The "assessment" score completely relies on the viewer's experience in radiographic interpretation and clinical knowledge. In contrast, the radiographic scoring system uses rigid guidelines for the evaluation of radiographic patterns. This technique reduces and standardizes the interpretation, but does not completely eliminate subjectivity. Additionally, the scoring system is weighted (e.g. alveolar scores have a greater impact than interstitial scores), and therefore considers the impact of pattern type on disease severity. This interpretation is based on radiographic – pathologic correlations ((Heitzman 1984; Toal and Cudd 1987) as well as subjective clinical experience.

5.1.1.1 Reproducibility of the equine neonatal radiographic scoring system

Three individual and blinded interpreters established the reproducibility of the radiographic scoring system in this study. Excellent correlation was determined for the regional radiographic scores of the cd, cv and crv regions, as well as the alveolar, alveolar-interstitial and total scores ($ICC>0.90$). The evaluation of the craniodorsal lung region appeared less consistent, which may be related to an abundance of intrathoracic structures obscuring interpretation of the craniodorsal pulmonary parenchyma. The assessment of the alveolar-interstitial score (added sum of alveolar score + interstitial score) was more reliable than the sole interpretation of the interstitial pattern, since transitions between radiographic patterns may occur. With increasing interstitial disease severity, reticulated opacities may develop and coalesce to form a solid, soft tissue density that is compatible with an alveolar pattern (Lester and Lester 2001). In order to assure maximum accuracy of our radiographic scores, we only included variables with an ICC>0.90 for further evaluation (Table 8).

5.1.1.2 Radiographic pattern and distribution

Fifty-nine percent of 128 neonatal thoracic radiographs (75/128) showed evidence of respiratory disease at the time of presentation in this study. In a previous report, Lamb et al determined that normal foals had clear lung fields within 12 hours of birth (Lamb, O'Callaghan et al. 1990). Lamb also noted that a more marked interstitial pattern was observed in immature and septic patients compared to healthy term foals, and a diffuse air-space (alveolar) pattern was seen in foals with respiratory distress syndrome (RDS). It was concluded that thoracic radiographs taken 24-48 hours after birth may aid differentiation of normal foals, septic or immature foals, and foals with RDS. Foals with RDS in the study by Lamb et al were either prematurely induced or delivered by cesarean section at a gestational age ≤ 310 days. Primary surfactant deficiency (RDS) was the suspected cause of respiratory failure in these patients (Lamb, O'Callaghan et al. 1990).

Radiographic abnormalities (regional scores > 1/6) in our study, were most frequently observed within the caudodorsal and caudoventral lung regions concurrently (47/75, 63%). The total number of foals with any abnormalities involving the caudodorsal lung region included 72/75 animals (96%, Table 9). Changes within the cranioventral lung were uncommon and were only observed in foals with diffuse radiographic disease [17/75]. These results complement findings by Lester et al, who previously stated that the caudodorsal lung is the most commonly affected region on initial radiographic evaluation, and the cranioventral region is the least affected area (Lester and Lester 2001).

Combined alveolar-interstitial disease was the most commonly observed radiographic pattern in our study (Table 11). Concurrent caudodorsal and caudoventral alveolar-interstitial radiographic changes were present in 45/75 foals (60%). Additionally, 17/75 foal (22.7%) showed diffuse alveolar-interstitial disease. These findings only stand in slight contrast to a previous study by Lester et al (Lester 1998), which described a predominance of diffuse interstitial disease. Prolonged lateral recumbency may lead to overinterpretation of interstitial radiographic infiltrates. However, our non-ambulatory foals are generally maintained in sternal recumbency prior to diagnostic imaging, to allow maximum oxygenation and ventilation in critical patients.

5.1.2 Discussion of part one: The association between selected clinical parameters and the type of pulmonary radiographic disease manifestation in neonatal foals

5.1.2.1 The systemic inflammatory response syndrome (SIRS)

Infectious neonatal respiratory diseases are usually part of a multiple-organ, systemic infection or SIRS (Paradis 1989). The term "systemic inflammatory response syndrome" (SIRS) is generally defined as the body's systemic inflammatory response to a variety of severe infectious or non-infectious clinical insults, as previously described (Committee 1992). When SIRS is the result of a confirmed infectious process, it is termed "sepsis". Since the clinical manifestations of sepsis are identical to those of SIRS, the differentiation of these conditions can be challenging, specifically in pretreated animals (Committee 1992). Bacteremia cannot always be confirmed in the face of sepsis, due prior antibiotic treatment, transient bacteremia, poor sampling or culture techniques. Wilson et al reported a negative blood culture rate of 19% in 47 confirmed cases of equine neonatal sepsis (Wilson and Madigan 1989).

Both a blood culture and modified sepsis score were obtained from 50/75 foals in this study. Survival rates were not significantly different between foals with a positive blood culture or sepsis score $\geq$ 11. Of 34/50 (68%) foals with a sepsis score $\geq$ 11, only 13 patients also had a positive culture (13/34; 38%). Overall, the percentage of positive blood cultures in this study was low (33%; 17/51; no blood culture performed in 24/75 foals), but comparable to the percentage of positive blood cultures obtained in the remaining population of hospitalized neonatal foals between 1990-1998 (44/140; 31%). Marsh et al also reported a positive blood culture in 28.5% (155/543) of neonatal foals admitted to a referral center (Marsh and Palmer 2001).

5.1.2.2 The impact of selected clinical parameters on pulmonary pattern

The evaluation of 12 selected clinical parameters in 75 foals in this study revealed that 31% of the variability in overall radiographic abnormalities (corrected total score) could be explained by a poor suckle reflex, fibrinogen concentration > 400mg/dL and tachypnea (Table 12). Interestingly, tachypnea and SIRS were related to increased radiographic abnormalities within the caudodorsal lung. Pulmonary ventilation and perfusion is closely matched in horses, and the percent regional blood flow is increased in the caudal lung lobes (Stewart, Young et al. 1987). Several studies demonstrate a minimal role of gravity in determining pulmonary blood flow distribution in horses. Seemingly, a dorsally increasing, vertical gradient of pulmonary ventilation exists in the horse that is matched by a similar gradient of perfusion (Amis, Pascoe et al. 1984). SIRS may initiate severe vascular leakage and thus contribute directly to the pathogenesis of lung injury in regions of increased relative blood flow.

The term “lung injury” is used to describe the pulmonary response to a wide range of injuries occurring either directly to the lung or as a consequence of injury or inflammation at other sites in the body (Bellingan 2002). The pathophysiology of acute lung injury (ALI) is driven by an aggressive inflammatory reaction. In the exudative phase, injury to the alveolar epithelial barrier leads to an increase in permeability to protein, extravasation of solutes and water. The resulting excessive fluid accumulation in airspaces can manifest as an alveolar-interstitial radiographic pattern (Pittet, Wiener-Kronish et al. 1995).

A high anion gap is frequently related to SIRS, due to increased concentrations of unmeasured anions such as lactate. Interestingly, an AG $\geq$ 20 mEq/dL was also associated with increased cd regional scores in a subset of foals with arterial blood gas results.

The presence of tachypnea also predicted higher radiographic scores within the caudoventral and cranioventral lung. Although tachypnea may be a nonspecific sign of pneumonia and is frequently associated with non-respiratory conditions (pain, fever, excitement, anemia), it was the most consistent clinical parameter to indicate radiographic pulmonary disease in this study.

The distribution of an abnormal pulmonary pattern may provide insight as to cause of the disease (Lester and Lester 2001). Primary alveolar disease was noted most frequently within the caudoventral lung of our neonatal foals (Table 10, cv only: 28%). A caudoventral alveolar distribution is highly suspicious of an inflammatory or pneumonic condition. Aspiration pneumonia (milk, meconium, gastric reflux etc.) is a common cause of caudoventral alveolar infiltrates in neonatal foals. In this study a poor suckle reflex was consistently related to an apparently paradoxical decrease in caudoventral radiographic scores. Evaluation of the clinical data revealed that this sub-population of critically ill neonatal foals with a poor suckle reflex, was invariably less than 4 days of age at the time of admission (76% < 1 day). Nutritional support was maintained through nasogastric intubation, therefore decreasing the risk for postnatal aspiration and caudoventral distribution of alveolar disease. Early hospital referral in the course of the disease may have further limited the extent of radiographic changes at the time of admission.

Foals with evidence of dyspnea, a sign of severe or advanced respiratory disease, showed consistently increased cranioventral regional scores. However, all foals with cranioventral radiographic disease also showed diffuse radiographic abnormalities. Additionally, cranioventral radiographic changes worsened over time in foals with evidence of pulmonary disease at the time of admission, while caudodorsal and caudoventral abnormalities improved. This finding supports the results of a previous study by Lester et al, who proposed that infiltrates tend to settle ventrally as the foal becomes ambulatory (Lester and Lester 2001).

5.1.2.3 Conclusion

In general, none of the clinical parameters could explain more than 31% of the variability in radiographic abnormalities, in this study. This finding reiterates the difficulty of diagnosing a pulmonary disease manifestation in neonatal foals without the use of advanced diagnostic techniques.

5.1.3 Discussion of part two: The impact of pattern recognition, distribution, and severity of pulmonary changes on short-term survival

In the second part of section one of our study, we explored the effect of pattern recognition, distribution and severity of radiographic changes on survival of neonatal foals. Euthanasia of foals may be performed due to financial constraints or the clinician's impression of futility of treatment. This discrepancy may introduce a significant bias in the survival analysis. We therefore compared all clinical and radiographic parameters between foals that were euthanized and those that died naturally. Since no statistically significant difference was observed between groups ($p>0.05$), natural death and euthanasia were not differentiated in the subsequent outcome analysis.

The categorical univariate (Chi-square) outcome analysis revealed that foals with diffuse radiographic changes were 3.6 times more likely to die than radiographically normal patients (Table 9). Additionally, foals with concurrent alveolar disease within the cd and cv lung regions were 3.8 times more likely to die than normal foals. In contrast, the odds of non-survival were similar for animals without alveolar disease, foals with alveolar changes limited to the cd lung region and normal patients (Table 10).

In order to evaluate the effect of radiographic disease severity on outcome, univariate and multivariate analyses were performed to associate all regional and total radiographic scores with survival of neonatal foals. The "assessment" score and corrected total radiographic scores were significantly different between survivors and non-surviving neonatal foals (Table

14). Additionally, radiographic infiltrates in the caudodorsal and cranioventral lung region were negatively associated with survival. The odds for non-survival were increased by a factor of 1.7 for every one unit increase in cd regional score after correction for all concurrent radiographic variables (95% CI: 1.2-2.6). Additional parameters did not retain statistical significance in the multivariate model. A similar observation was reported by Lester et al, who associated increased severity of cd radiographic infiltrates with decreased survival rates in neonatal foals (Lester 1998). Severe disease within the caudodorsal lung region therefore appeared to be consistently associated with decreased survival rates in neonatal foals in our study.

5.1.3.1 Radiographic changes over time

Eleven percent of our foals (14/128) showed normal thoracic radiographs upon presentation, but developed pulmonary infiltrates on follow-up films. These increased opacities were most commonly related to more pronounced interstitial lung infiltrates. In acute lung injury (ALI), the thoracic radiographic abnormalities tend to follow a predictable sequence, relating to the underlying histopathological changes (Desai 2002). In the first 24 hours following insult, the thoracic radiographs are generally normal, as the earliest stage of the exudative phase of ALI has little if any alveolar edema. As lung injury evolves, increasing interstitial lung density will obscure lung markings and may eventually lead to alveolar infiltrates on thoracic radiographs (Desai 2002). This finding reiterates the importance of repeated diagnostic imaging.

5.1.3.2 Conclusion

Radiographic findings may either precede or lag behind alterations in respiratory function. In contrast to the adult horse, neonatal foals can develop significant respiratory disease over a very short time (Lester and Lester 2001). Likewise, the rate of resolution can be rapid, which indicated a favorable outcome in our study. Finally, it should be reiterated that our results were derived from an analysis of retrospectively gathered data, and that this study was designed to identify and explore potentially important clinical relationships and not to test a hypothesis.

In summary, the presence of dyspnea and fibrinogen concentration > 400 mg/dL suggested cranioventral radiographic changes, while SIRS was associated with caudodorsal disease in this study. In addition, tachypnea was most consistently related to diffuse (cd, cv and crv) pulmonary changes. Therefore, these parameters may potentially serve as indicators or risk factors of radiographic respiratory disease and alert the clinician to initiate early radiographic evaluation. The caudodorsal lung region was most commonly affected in our foal population and related to decreased survival rates.

5.2 Discussion of section two: Risk factors and prognostic variables for survival of foals with radiographic evidence of pulmonary disease

Section two of our study explored clinical indicators and prognosis of foals with neonatal thoracic radiographic changes in a referral center [TUSVM]. Respiratory involvement was chosen because an earlier study reported a 50% prevalence of pulmonary disease in hospitalized neonatal foals with a 39% survival to discharge (Freeman and Paradis 1992). The onset of the pulmonary component of a neonatal disease may be insidious and therefore difficult to diagnose by physical examination alone.

5.2.1 Discussion of part one: Clinical variables, which may predispose neonates or indicate respiratory disease

We isolated several parameters that were positively related to radiographic evidence of lower respiratory disease. Upper airway pathology, failure of passive transfer (FPT) and hypoxemia (P_aO_2 < 60 mmHg) were significantly associated with radiographic abnormalities in the univariate analysis ($p<0.05$, Table 15). Only FPT (IgG concentration ≤ 400 mg/dL), however, retained statistical significance after adjustment for the effects of other covariates in the multivariate model. Failure of passive transfer is a well known risk factor of neonatal infection, with similar relevance to respiratory disease.

Similar to section one, the term SIRS in this study was used to include patients with a modified sepsis score ≥ 11 (Brewer and Koterba 1988; Brewer, Koterba et al. 1988), a positive blood culture or a known focus of systemic infection. The sepsis score incorporates a combination of historical, clinical and laboratory variables which are used to establish the likelihood of neonatal infection. The development of the scoring system was originally based on a relatively small number of foals (Brewer and Koterba 1988). Although the sensitivity and specificity was favorable in a subsequent study (Brewer, Koterba et al. 1988), the uncritical use of the sepsis score as a definition of sepsis rather that SIRS still remains controversial.

Both a blood culture and modified sepsis score were obtained from 104 foals in this study. Neither a positive blood culture nor sepsis score ≥ 11, were associated with radiographic pulmonary disease in this population. Interestingly, foals with a sepsis score > 11 (57/104) were significantly more likely to die than foals with a normal sepsis score (47/104; p=0.031). A positive blood culture (34/104), however, had no significant effect on survival. Of 57/104 (55%) foals with a sepsis score ≥ 11, only 33% (19/57) also had a positive culture. Overall, the percentage of positive blood cultures in this study was low (32 %; 34/106 foals; no culture performed in 57/163 foals), but comparable to the percentage of positive blood cultures obtained in the remaining population of hospitalized neonatal foals between 1990-1998 (44/140; 31%). In a separate study Marsh et al reported positive blood culture results in 28.5% (155/543) of neonatal foals admitted to a referral center (Marsh and Palmer 2001).

5.2.2 Discussion of part two: Clinical variables, which may predict survival of foals with radiographic evidence of pulmonary infiltrates

In the second part of section two of our study, we isolated several parameters that were significantly related to outcome of foals with radiographic respiratory disease (univariate analysis; Table 16). 21/38 [55 %] foals were euthanized, while 12/38 [32%] died naturally during their time of hospitalization [5/38 undefined]. Termination of treatment may generally be related to financial constraints or the clinician's impression of futility of treatment. This discrepancy may introduce a significant bias in the statistical analysis. We therefore compared all clinical parameters between foals that were euthanized and those which died naturally. Since no statistically significant difference was observed between groups (p>0.05), natural death and euthanasia were not differentiated in the subsequent outcome analysis.

5.2.2.1 Dystocia and perinatal asphyxia syndrome (PAS)

Evidence of dystocia or depression upon presentation significantly increased a foal's chance of non-survival. Depression is frequently observed in the critically ill neonatal foal and may not relate to life-threatening respiratory disease but rather pertain to systemic signs of disease manifestation such as SIRS, sepsis or HIE. Dystocia may contribute to peri-parturient respiratory complications, as a result of perinatal asphyxia and indirect lung injury (extrapulmonary acute lung injury). In utero asphyxia related to dystocia may further lead to the expulsion of meconium and secondary inhalation of contaminated amnionic fluid (aspiration pneumonia). Though meconium may be sterile, it creates mechanical airway obstruction, surfactant inactivation and pulmonary inflammation, caused by chemotactic cytokines and vasoactive mediators (Klingner 1999). This predisposes the foal to severe respiratory complications post partum. More importantly, however, dystocia, maternal illness, fetal factors (e.g. twinning, aspiration, SIRS, sepsis, prematurity) and placental insufficiency are associated with perinatal asphyxia in foals (Furr 1996).

The presence of dyspnea (moderately increased respiratory effort) was significantly correlated with non-survival and frequently indicated severe or terminal respiratory disease (Table 17). Respiratory effort, rather than rate, is of clinical value when assessing disease severity in the newborn foal. The signs may present clinically as flared nostrils, excessive rib retraction and/or paradoxical breathing.

5.2.2.2 Impact of creatinine on neonatal survival

An increased creatinine concentration (>1.7 mg/dL) was significantly associated with higher mortality rates in our foal population ($p=0.002$), while hyperkalemia (K>4.7 mEq/L) did not obtain statistical significance ($p=0.086$). Changes in potassium and creatinine concentration were positively correlated ($p<0.001$) and may have indicated decreased urinary excretion of potassium due to volume depletion, which is commonly observed in systemic disease of neonates. The presence of an increased creatinine concentration retained a statistically significant association with non-survival after correcting for hyperkalemia ($p=0.015$) in this study. The odds of survival were increased 3.8 fold (95% confidence interval: 1.3-11) in foals with a creatinine concentration $\leq$ 1.7 mg/dL, after correction for potassium.

The creatinine concentration can vary extensively with age, activity level, hydration status and renal function. Although newborn foals routinely have creatinine concentrations 30% to 50% higher than those measured in the mare, it was interesting to note that the creatinine concentration in our population retained their statistical significance after correction for age, using a multivariate logistic regression model. High values in newborn animals are usually associated with high concentrations of creatinine in fetal fluids. These may further increase with urination during fetal distress and swallowed fetal fluid. Limited diffusion of creatinine across the placenta may also lead to marked creatinine elevations, observed in asphyxiated and premature foals (Reed) and may suggest lower survival rates.

Low creatinine concentrations have not been noted to correlate significantly with survival of septic foals (Gayle, Cohen et al. 1998). After the first week of life, creatinine is actually lower in foals than in adult horses and should at this time be considered as a primary indicator of hydration, renal and post-renal function.

5.2.2.3 Other clinical and laboratory data

The majority of physical examination parameters, which are usually obtained during the general respiratory evaluation of foals (e.g. evaluation of tachypnea, abnormal respiratory sounds, fever, weakness and milk reflux from the nares) were unrelated to outcome. These clinical variables are considered to have little prognostic value in the assessment of disease severity. This is particularly true for thoracic auscultation, since foals with no auscultable respiratory abnormalities may still have severe pulmonary disease. Gayle et al established a positive correlation between respiratory rate and survival of foals with sepsis (Gayle, Cohen et al. 1998). Additionally, neutropenia and leukopenia have also been associated with non-survival in septic foals (Barton, Morris et al. 1998; Gayle, Cohen et al. 1998). Both Gayle and Barton et al based the antemortem diagnosis of sepsis on a positive blood culture or a sepsis score ≥ 11, while Gayle also included foals with evidence of multisystemic infectious disease. In our study, 70/121 (58.9%) foals with radiographic abnormalities were diagnosed with SIRS. However, the presence of SIRS did not significantly impact survival (p=0.079).

5.2.2.4 Arterial blood gas analysis

The impact of arterial blood gas parameters on neonatal survival was evaluated in a subset of 67 foals with obtained arterial blood gas results. The analysis of a population subset was considered to introduce minimal bias, since the prevalence of any selected clinical parameter (Table 7) was not significantly different between foals with or without arterial blood gas results.

5.2.2.5 The effect of anion gap (AG) on survival of neonatal foals with radiographic respiratory disease

An interesting finding was the association between anion gap and death, which had been previously observed by Hoffman et al in the evaluation of survival in critically ill neonatal foals (Hoffman, Staempfli et al. 1992). In our study, acidemia and high anion gap values were significantly associated with non-survival in the univariate analysis. In the multivariate model, the risk for non-survival increased 11.3 fold (95% confidence interval: 3.3-39.4; p<000.1, n=58/67) in foals with an anion gap ≥ 20 mEq/L, if all other blood gas parameters remained equal.

High anion gaps occur if there are increased serum concentrations of unmeasured anions (volatile fatty acids, lactate, pyruvate, sulfates and phosphates) or decreases in the concentration of unmeasured cations (calcium, magnesium) (Lorenz JM 1999). Relevant decreases in unmeasured cations are uncommon (Lorenz JM 1999), as verified by our lack of any significant association between anion gap and hypocalcemia (p=0.279). Although lower globulin and albumin concentrations may decrease the anion gap, a significant interaction between anion gap and globulin or albumin concentrations was not observed in our foal population. Magnesium values were not available in this study, while hyperphosphatemia was only noted in 4/121 (3.3%) patients and subsequently eliminated from further analysis. Hyperkalemia and a creatinine concentration > 1.7 mEq/L were related to a high anion gap ($p \leq 0.05$). One may, therefore, speculate that altered renal function or perfusion may have reduced the excretion of unmeasured anions in some foals. The presence of SIRS, dystocia, and acidemia were also significantly associated with an anion gap ≥ 20 mEq/L in our study ($p \leq 0.05$). In the presence of acidemia, an elevated anion gap usually indicates an organic acidosis (Lorenz JM 1999), or lactic acidosis.

Blood lactate levels were not measured in this study. Further statistical analysis of blood gas results was therefore performed to investigate if lactic acidosis may have increased anion gap values. The P_aCO_2 showed a negative linear correlation with arterial pH ($p<0.001$) and a positive linear correlation with arterial bicarbonate values ($p<0.001$). In short, as P_aCO_2 increased, a correlated decrease in pH and increase in bicarbonate was observed. Based on these findings, the primary arterial blood gas abnormality in these foals appeared to be a respiratory acidosis with a metabolic compensation. Additionally, the descriptive blood gas analysis revealed that 29/40 patients (72.5%) with a primary acidemia were diagnosed with a respiratory acidosis, while a metabolic acidosis was noted in only 5/40 (12.5%) and mixed acid-base changes in 6/40 (15%) animals. A report by Aberman and Hew demonstrated that the initial arterial blood gas values in patients with chronic obstructive pulmonary disease may show a pattern of acute respiratory failure with no metabolic disturbance. The increased anion gap in these patients, however, indicated the presence of a metabolic acidosis, which was then confirmed with the measurement of serum lactate (Aberman and Hew 1978). Mountain et al further determined that metabolic acidosis is a common finding in acute, severe asthma and suggested that the pathogenesis of lactic acidosis in respiratory disease is multifactorial and includes contributions from lactate production by respiratory muscles, tissue hypoxia, and intracellular alkalosis (Mountain, Heffner et al. 1990). Severe arterial hypoxemia (P_aO_2, ≤ 55 mmHg) was related to AG values ≥ 20 mEq/L in our study (p=0.058). P_aO_2 ≤ 55 mmHg is commonly associated with decreased arterial oxygen saturation, which could limit peripheral oxygen delivery. Lactic acidemia ensues due to decreased peripheral perfusion, inadequate oxygen delivery and tissue uptake (decreased O_2 diffusion capacity), increased tissue lactate production as well as inadequate hepatic and renal lactate extraction (Harris, Musher et al. 1987).

In the fetus, lactate can serve as an energy source and may also be increased in animals at birth if they have been compromised in utero (e.g. placental insufficiency). Additionally, increased lactate can be a measure of multiple organ dysfunction, rather than respiratory injury alone. Lactic or high anion gap acidosis caused by decreased oxygen delivery or defective oxygen utilization has been associated with high mortality rates (Ishihara and Szerlip 1998), and may have therefore contributed to non-survival in our neonatal foals.

SIRS was the most common diagnosis in our population of foals with radiographic evidence of respiratory disease (70/121, 58.9%). Additionally, SIRS was associated with a high anion gap (p=0.026). However, we propose that lactic acidosis related to SIRS or sepsis was not the primary cause of anion gap elevation in these foals with thoracic radiographic changes. As previously noted, a respiratory rather than metabolic acidosis was primarily observed on blood gas analysis. Additionally, the anion gap was linearly correlated with the severity of radiographic changes, which were graded by a score of 1-6 (p=0.012) as described previously. It therefore appears plausible that the increase in anion gap in these foals may have resulted from oxygen deficits and lactic acidosis related to respiratory disease, in addition to underlying sepsis, SIRS or a primary metabolic derangement.

5.2.2.6 Conclusion

The final model of our survival study included foals with the following criteria: history of dystocia, dyspnea and a creatinine concentration > 1.7 mg/dL. An anion gap ≥ 20 mEq/dL was strongly correlated with non-survival in a subset of foals with arterial blood gas results. These variables represent clinical and hematological parameters that can be readily obtained during the initial patient evaluation. The presence of a high anion gap appeared to have the greatest clinical impact and may be a useful prognostic parameter in patients with radiographic evidence of respiratory disease. Failure of passive transfer (IgG ≤ 400 mg/dL) was the only multivariate risk factor for thoracic radiographic changes in this study. This finding reiterates the difficulty of diagnosing a pulmonary disease manifestation in neonatal foals without the use of advanced diagnostic techniques.

5.3 Study limitations

The design of our study was retrospective and we, therefore, relied on the accuracy and completeness of medical records. Several clinical variables were not available for a large number of foals and could not be statistically analyzed. Nonetheless, the multivariate model was useful to identify prognostic variables and to assess the association of a given covariate. The small number of foals in the study and the adjustment for confounding effects of other variables in the model may, however, have influenced the reliability of the odds ratios. Additionally, not all foals that were admitted to the hospital had thoracic radiographs taken. This study, therefore, does not include foals that may have shown signs of respiratory disease but did not have radiographs taken within 48 hours of admission. Only foals with a radiographic manifestation of respiratory disease at one or more time points during their hospitalization fulfilled our selection criteria of “pulmonary disease”.

All diagnostic radiographs were obtained either in right lateral recumbency or in the standing position of the animal with the right thorax closest to the radiographic cassette (section II). Unfortunately, radiographs in left lateral recumbency were not available for this study. This may have limited the sensitivity of our diagnostic evaluation, since the severity of radiographic abnormalities is significantly dependent on patient position. Unilateral lesions of the right hemi-thorax during right-lateral recumbency (less aerated “down lung”) may have, therefore, been underestimated using our described diagnostic technique.

5.4 Clinical significance

Early thoracic radiographic imaging of compromised neonatal foals may alert the clinician and establish a prompt diagnosis of underlying respiratory disease. Since radiographic findings may precede or lag behind alteration of respiratory function, repeated diagnostic imaging is recommended. The presence of dyspnea, tachypnea, a fibrinogen concentration > 400 mg/dL, SIRS, hypoxemia and failure of passive transfer in neonatal foals may be suggestive of underlying respiratory disease and should prompt an early radiographic evaluation of the thorax, even in the absence of other localizing clinical signs.

Radiographic abnormalities involving the caudodorsal lung region were most common in our foal population. The presence of diffuse radiographic infiltrates (caudodorsal, caudoventral and cranioventral involvement) or concurrent alveolar patterns within the caudodorsal and caudoventral lung may alert the clinician of lower survival rates. Additionally, a history of dystocia, dyspnea, a creatinine concentration > 1.7 mg/dL and an anion gap of ≥ 20 mEq/dL on arterial blood gas analysis, may reduce survival chances. Aggressive medical management, early fluid resuscitation and specific respiratory support may be crucial for the successful outcome of these patients.