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Article

Diagnosis, Mortality Rates and Risk Factors Among Neonatal Foals Admitted to a Veterinary Teaching Hospital in Israel Between the Years 2018-2020

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Simple Summary

Foals are at high risk of dying during the first few days of life. To help both owners and clinicians make informed decisions, we describe the various diagnoses and outcomes of 200 neonatal foals that were referred to a Veterinary Teaching Hospital for treatment. Most foals (50%) were three days old on admission. They were most commonly of the Arabian horse breed (82.4%) and there were more fillies (66%) than colts (34%). The top three diagnoses on admission were sepsis, a serious life-threatening infection (22.5%), diarrhea (20.5%) and infection of the umbilicus (17%). One out of every four foals (24.5%) either died or had to be euthanized. Foals diagnosed with sepsis by the clinician on admission were 4 times more likely to die or be euthanized compared to foals that were not. These findings can help both owners and veterinarians make important decisions, but require caution in making conclusions, since populations may differ between regions or hospitals.

Abstract

In horses, the risk of death is greatest during the first days of life. The objectives of this study were: 1) To describe the distribution of diagnoses and the case fatality rates among neonatal foals. 2) Within the septic foal population, to identify potential risk factors for mortality. Two hundred cases were included in the study. The median age on admission of the foals in the general population was 72 hours. The Arabian horse was the most common breed (82.4%). The general mortality rate was 24.5%, (95% Confidence Interval (CI): 18.7-31.1). The top three diagnoses on admission were sepsis (22.5%), diarrhea (20.5%) and omphalitis (17%). Of the entire population of foals, 43% (95% CI: 36-50.2) were classified as septic by use of the definition in this study. The median age of septic foals on admission was 96 hours. The most common breed was Arabian (82.7%). The mortality rate among the septic foals was 30.2% (95% CI: 20.8-41.1). A foal that was diagnosed with sepsis on admission, was 4.3 times more likely to die or be euthanized compared to a foal that was not diagnosed with sepsis on admission.

Keywords: horse; foals; sepsis; mortality rates

1. Introduction

Treating a neonatal foal in an intensive care unit is labor intensive, relatively expensive, and often stressful for the owners (1). Prognosis for survival has improved over time, as was reported in a large-scale study from the USA. The adjusted odds of survival for foals admitted in the 2000s were approximately 3.4 times higher than that of foals admitted in the 1980s (2). Still, despite considerable progress in the care of hospitalized foals, the risk of death remains substantial. A recent study from Belgium reported a fatality rate for hospitalized neonatal foals of 33.3% (3). Veterinarians are often requested by the owners to provide prognoses for these foals before referral as well as during the early stages of hospitalization. Such decisions depend on signalment, case history, physical

examination, clinicopathological data, as well as knowledge provided by previously published data. To enable better decision-making, knowledge of the prognoses of specific pathologies is required, but this may vary between countries, facilities and over time. Specific studies might not be applicable to other equine neonatal intensive care units, due to differences in referral populations, case distribution and treatment protocols as suggested by Giguère et al., 2017 (2). The severity of the disease at the time of admission, which is dependent on both owners and referring veterinarians, also affects survival of these foals. Population characteristics of horses differ between countries, which affects the prevalence of different pathologies and also affect the outcome. Data regarding the prevalence of different pathologies, among neonatal foals in our region, is limited.

The objectives of this study were: To describe the distribution of diagnoses and the case mortality rates among neonatal foals admitted to the Koret School of Veterinary Medicine, Veterinary Teaching Hospital (KSVM-VTH), Israel, from birth to 14 days of age and to identify potential risk factors for mortality in the septic foal population on admission to the hospital.

2. Materials and Methods

This study was a retrospective cohort study involving all cases of neonatal foals from birth to 14 days of age admitted to the KSVM-VTH between the years 2018-2020. Data collected included; history and physical examination findings, blood test results and bacterial cultures obtained from samples of joints and umbilici. This information was extracted from the hospital digital medical records program (Chameleon, Elad Software) and arranged in an Excel file (version 1.5, © 1985-2003 Adobe Systems Incorporated). Diagnoses on admission (possibly more than one) were routinely documented by the receiving clinicians at the hospital following a basic diagnostic workup (clinical signs, blood test and ultrasound) and clinical assessment. Quantitative values that were recorded as descriptive parameters in the files (e.g., low, normal, high) were converted to a quantitative value based on clinical experience: "slow heart rate" was converted to 76 bpm and "normal" as 100 bpm. "Normal respiratory rate" was converted to 26 bpm and "tachypnea" to 80 bpm. Urea (mg/dL) recorded as "< 20" was considered normal. Since the association between neutrophil counts and sepsis is not linear, neutrophil counts were categorized (0-3) as per the definitions of the original Sepsis Score (4). Neutrophil toxicity was subjectively evaluated. Band neutrophil count was assessed qualitatively rather than quantitatively and hypoglycemia was defined as 50 mg/dL. When exact gestational age was unavailable, normal gestational age was documented as 345 days. "Several hours of age" was documented as four hours. Attitude was classified as normal or abnormal (e.g., hypotonia, coma, depression or seizures). Foals diagnosed with sepsis were defined according to the criteria outlined below, and analyses of risk factors for mortality were conducted exclusively on this defined population. The study was approved by the Hebrew University Ethics Committee (HU-NER-2020-033-A).

2.1. Septic Foal Classification

Based on Wong's classification of sepsis (5) and on the equine neonatal Systemic Inflammatory Response Syndrome (SIRS) criteria, and adapted to the variables examined at KSVM-VTH, sepsis was defined as:

Presence of more than one of the following criteria: infected joints, omphalitis (based on ultrasound morphological appearance or positive umbilical culture), and signs of diarrhea (loose, watery stools). This was adapted from Wong's classification of sepsis.

Or:

Adapted from SIRS criteria: presence of at least three of the following five criteria; heart rate > 120 beats per minute, respiratory rate > 30 breaths per minute, glucose < 50 mg/dL, abnormal temperature ($T > 38.8^{\circ}\text{C}$ or $T < 37.7^{\circ}\text{C}$) or leukocyte count (white blood cells (WBC) $< 4.3 \times 10^3/\text{mm}^3$ or $\text{WBC} > 14.8 \times 10^3/\text{mm}^3$). At least one of the latter two criteria was required.

2.2. Statistical Analysis

The entire population of foals admitted to the KSVM-VTH, as well as the subset classified as septic, were summarized and characterized by descriptive statistics. The distribution of continuous variables was assessed for normality using the Shapiro–Wilk normality test and were reported as medians and quartiles. Frequencies were reported as percentages and 95% confidence intervals. Short term mortality was defined as death occurring during hospitalization. Foals identified as septic based on the study’s previously defined criteria were included in the analysis of risk factors for short term mortality. The Mann–Whitney U test was used for univariable analyses of continuous variables. Categorical variables were analyzed using either the chi-square test or Fisher’s exact test, with Fisher’s exact test applied when expected cell counts in one or more cells were <5. Variables of clinical and laboratory parameters on admission that demonstrated a statistically significant association with short-term mortality ($p < 0.05$) by univariable analysis in the population of septic foals were further assessed using a multivariable logistic regression model. To reduce multicollinearity, variables with strong intercorrelations (Spearman’s $\rho > 0.9$) or significant associations based on Fisher’s exact test ($p < 0.01$) were excluded from the multivariable model by choosing to exclude those of less significant p-values. The final multivariable logistic regression model was constructed using a forward stepwise likelihood-ratio selection procedure. IBM SPSS versions 27 and 31. WinPEPI Describe A (version 3.18) was used to calculate Confidence Intervals (CI) for descriptive proportions.

3. Results

3.1. General Population Description

Two hundred cases were included in the study. The entire study population included 132 females (66%) and 68 (34%) males. The median age of the foals was 72 hours, and the lower and upper quartiles were 24 and 126 hours. The median gestational age was 345 days (quartiles: 331 and 345 days) but this information was available only for n=119 foals. The Arabian horse was the most common breed (82.4%). Of 200 foals, 151 foals were discharged alive (75.5%, 95% CI: 0.69-0.81), 36 died (18%) and 13 were euthanized (6.5%).

3.2. Distribution of Diagnoses

The frequency of the more common diagnoses on admission to the hospital and their case fatality rates are presented in Table 1 (multiple diagnoses per foal were recorded). Most frequent diagnoses on admission were sepsis (22%), diarrhea (20.5%) and omphalitis (17%). Other less common diagnoses that were not included in the tables were: laryngeal/pharyngeal weakness, congenital patellar luxation, uroperitoneum, aspiration pneumonia, small intestinal intussusception, meconium impaction, angular limb deformity (carpal valgus), prematurity/dysmaturity, weakness, seizures, foal rejection by the mare and more.

Table 1. Distribution of common clinical diagnoses on admission to the hospital (n=200) and case fatality rates for each diagnosis. Multiple diagnoses could be assigned per foal. [FPT – failure of passive transfer; NMS – neonatal maladjustment syndrome].

Diagnoses	Percentage (n; %; 95% CI*)	Case Fatality (n; %; 95% CI*)
Sepsis	44; 22.5 (16.5-28.4)	14; 31.8 (18.6-47.6)
Diarrhea	41; 20.5 (15.1-26.8)	4; 9.8 (2.7-23.1)
Omphalitis	34; 17 (12.1-22.9)	3; 8.8 (1.9-23.7)
FPT	25; 12.5 (8.3-17.9)	2; 8.0 (1.0-26)
NMS	16; 8 (4.6-12.7)	3; 18.8 (4.1-45.7)

*CI=Confidence Intervals.

3.3. Septic Population Description

The septic foal population (as defined retrospectively) included 86 of the 200 cases (43%). There were 56 (65.1%) females and 30 (34.9%) males. The median age on admission (quartiles) was 96 hours

(36, 144) (n=81). The missing data are from cases in which “several days” was documented and not a specific number. The median gestational age was 345 days (331, 345) (n=49). The most common breed among the septic foals was Arabian (82.7%). The description of clinical findings and blood values is presented in Table 2. Neutrophil toxicity was described as normal (19.4%), mild toxicity (16.4%), moderate toxicity (29.9%) and severe toxicity (34.3%). Left shift of neutrophils was recorded as normal (63.6%), slight left shift (13.6%) and marked left shift (22.7%). Among septic foals, 60 foals were discharged alive (69.8%), 22 died (25.6%) and four were euthanized (4.6%).

Table 2. Median (quartiles) of clinical findings and blood values in septic foals. The number of foals included for each parameter (n) is presented.

Parameter	Median (Quartiles)	Number of foals (n)
Clinical parameters		
Heart rate (bpm)	120 (96, 140)	85
Respiratory rate (bpm)	36 (26, 48)	83
Body temperature (°C)	38.2 (37.7, 38.9)	82
CBC		
Hematocrit (%)	41.4 (36.5, 46.6)	76
Platelets (X10 ³ /μL)	137.5 (86.2, 180.7)	76
WBC (X10 ³ /mm ³)	5.6 (3, 9.6)	83
Neutrophils (X10 ³ /μL)	4.4 (2.3, 8.2)	76
Biochemistry		
Sodium (mmol/L)	137.9 (136, 142.2)	79
Potassium (mmol/L)	3.6 (3.2, 4.0)	79
Chloride (mmol/L)	99 (96.5, 102.4)	79
Glucose (mg/dL)	86 (42.2, 119.7)	60
Urea (mg/dL)	45.3 (23.6, 62.4)	22
Creatinine (mg/dL)	1.3 (1.0, 2.1)	75

3.4. Parameters Associated with Death Among the Septic Foals by Univariable Analysis

Clinical findings and blood values associated with death are presented in Table 3. Diagnoses associated with death are presented in Table 4.

Table 3. Clinical findings and blood values associated with death by univariable analysis (p-value) and the direction of change associated with death for significant parameters.

	P value	Change associated with death
Clinical parameters		
Age	0.514	--
Gestation age	0.898	--
Breed	0.764	--
Sex	1.0	--
Heart rate	0.628	--
Respiratory rate	0.378	--
Capillary Refill Time (CRT)	0.009	Prolonged
Mucous membranes	0.0002	Abnormal
Attitude	0.00001	Abnormal
Blood parameters		
Leukocytes (X10 ³ /mm ³)	0.032	Decrease
Thrombocytes (mmol/L)	0.016	Decrease
Sodium (mmol/L)	0.006	Increase
Potassium (mmol/L)	0.029	Increase

Glucose (mg/dL)	0.0003	Decrease
Monocytes (X10 ³ /μL)	0.651	--
Lymphocytes (X10 ³ /μL)	0.645	--
Neutrophil count (categories 0-3) (0-3)	0.0006	Decrease
RBC (X10 ⁶ /mm ³)	0.5	--
Hematocrit (%)	0.894	--
Hemoglobin (g/dL)	0.874	--
Creatinine (mg/dL)	0.151	--
Chloride (mmol/L)	0.2	--
Calcium (mmol/L)	0.634	--
Neutrophil toxicity	0.443	--

Table 4. Diagnoses on admission significantly associated, on univariable analysis, with short term death among the septic foals (n=86), the p-value of the association and the direction of the association with survival.

Diagnoses	P value	Association with survival
Sepsis	0.017	Decrease
Omphalitis	0.028	Increase
Diarrhea	0.048	Increase

3.5. Multivariable Analysis of Factors Associated with Death Among Septic Foals

Parameters included in this test: Neutrophil count in categories (0-3), platelet count (x10³/μL), sodium (mmol/L), potassium (mmol/L), glucose (mg/dL) and attitude (normal vs abnormal). WBC was not included as it was found to be strongly associated with neutrophil counts (rho=0.98). Neutrophil count was included due to a lower p-value than WBC on univariable analysis of the association with short term mortality. Capillary Refill Time (CRT) and mucous membrane color were strongly associated with attitude (p<0.03) and were therefore not included in the multivariable model. Attitude was chosen due to its lower p-value in association with short term mortality (p=0.00006). The final multivariable regression model had a Nagelkerke R-square of 0.45 and improved the prediction of the model from 70% to 86%. Due to the large number of cases missing glucose values, the model included only 58% of the cases (N=50), however, while removal of the parameter glucose, resulted in the inclusion of 84% of the cases, the change in the results was minor but the model was less strong (based on Nagelkerke R-square and change in prediction). The results are presented in Table 5. On multivariable analysis of the septic foals (n=86), including only the three diagnoses on presentation associated with short term death among the septic foals on univariable analysis, those diagnosed as septic on admission retained a statistically significant association with death with an odds ratio of 4.3 (95% CI: 1.2-15.5).

Table 5. Factors significantly associated with short term death on multivariable analysis within the subset of foals diagnosed as septic. The p-value of the association, the odds ratio and 95% Confidence Interval (95%CI). N=50.

Factors associated with death	P value	Odds ratio (95% CI)
Attitude (abnormal vs. normal)	0.006	9.7 ^a (1.9, 48.6)
Potassium (mmol/L)	0.02	6.5 ^b (1.3, 32.5)

^aAbnormal attitude increases odds of death by 9.7. ^bFor every unit increase in potassium, the odds of death increase by 6.5 times.

4. Discussion

In this study we aimed to describe the distribution of diagnoses of neonatal foals admitted to the KSVM-VTH. Currently, this is the only equine hospital in the country in which foals are hospitalized. For the referring veterinarian it would be interesting to note that the most common diagnoses made

by the receiving clinicians on admission (potentially including more than one) were sepsis (22.5%), diarrhea (20.5%), omphalitis (17%), FPT (12.5%) and NMS (8%) and that diarrhea and omphalitis carried better prognoses than other diagnoses. This information regarding diagnoses together with the prognoses for these conditions, contribute to the decision-making process when faced with similar cases. However, it is important to consider that the majority of the foals were assigned one or two diagnoses at the time of admission.

The finding that the prevalence rate of sepsis (based on the definition of sepsis in this study) of 43% (95% CI: 36-50.2) was twice that of the prevalence rate of sepsis recorded by the receiving clinicians on admission (22.5%), has been previously reported (2). A large animal hospital at the University of Florida reported that only 113 foals (10.6%) were categorized as septic as a primary diagnosis in the records, whereas 60.2% met the criteria for sepsis, as were determined in that study by the authors (positive blood culture and more than one site of infection) (2). Classification of sepsis is indeed challenging, and differs between studies, which results in different prevalence rates. For example, the prevalence of sepsis was 27% in a study from Denmark and Sweden (6), and higher in studies from the USA (5) and Belgium (3) (46% and 43.9% respectively). In a recently published large scale study, that included data on 1068 critically ill neonates, from 16 veterinary referral hospitals in four countries, the authors reported that the ability to predict infection using history, signalment, physical examination findings, laboratory results, and SIRS-related indices was poor to fair (7). Diagnosis of sepsis on admission is, therefore, complicated. Improved definitions for this stage of case management are required.

The rate of the initial presenting sign of diarrhea (20.5%; 95% CI:16.9-28.9) of the foals in this study is similar to the rate reported in one of two studies from the USA 25.7% (2) but significantly lower than in the other (33.4%) (8), based on the 95% confidence interval. Enteritis was reported in 14% of the foals in a recent study from Belgium (3). Since the clinical sign of enteritis is diarrhea in a foal, and since it is probable that some of the foals for which diarrhea was written in the records as a primary diagnosis were septic, as was also reported recently (3), comparisons between studies and populations are challenging.

The prevalence rate [8% (4.6-12.7)] and case fatality rate for NMS in this study [18.8% (4.1-45.7)] was not significantly different from these rates in foals in Belgium (8.6%, with 26.3% case fatality) (3). However, in studies from the USA, the prevalence of NMS was significantly higher (14.6%) but with a similar case fatality rate to two studies, 20% (2) and 14.9% (8). Mortality in foals diagnosed with NMS depends on the timing of the appearance of the clinical signs. When they appear 6-24 hours after delivery, the prognosis is good, but when they appear at birth, the prognosis is poor. It also depends on the presence of major complications, such as sepsis (9). The prognosis of the foals in this cohort could be considered relatively good, since all but one of the foals in this cohort were between 6 and 24 hours old. However, the age in this study was the age of the foals at presentation at the hospital and not the age at which the signs first appeared.

The foal population in this study differs from others reported in the literature in that they are predominantly Arabian fillies. The most common breed was the Arabian horse (82.4%), which is one of the oldest horse breeds in the history of humankind (10), and has high financial value. The fact that more females (66%) than males were admitted to the hospital might also be related to their higher financial value as future broodmares. This is different from the foal population in two studies from the USA, in which the main breed was Thoroughbreds, with only a few Arabian horses and colts were more prevalent than fillies (2, 8). This is also different from the population in three studies from Europe, where Warmbloods was the common breed and colts were also more prevalent (3, 6, 11). Such differences between the populations may lead to different outcomes. For example, some of the pathologies in neonatal foals are more common in specific breeds and in a particular sex. In regards to breed, foal rejection is relatively common in the Arabian breed (12), possibly leading to FPT and sepsis. In regards to sex, ruptured bladder is more common in colts (13).

Short term survival in our study was 75.5% (95% CI: 69-81), which was higher than the survival rates that were reported previously: 66% in South Africa (14), 66.7% in Belgium (3), 67% in the USA

(15), but comparable to one study from the USA 72.8% (2) and one in Denmark 71.6% (11) and significantly lower than another study (82.1%) in the USA (8) and another from Denmark and Sweden (83%) (6). These differences are very small, however. The relatively good prognosis in this study is likely the result of increased awareness and early referrals by both the owners and the referring veterinarians in the country (16) as well as the specialized training of the clinicians.

Sepsis, which is defined as the concurrent evidence of SIRS and the identified or suspected presence of microbial infection, is a common cause of morbidity and mortality in neonatal foals (7). The mortality rates among septic foals reported in the literature are highly variable, but in general, the outcome has improved significantly over time, which is likely due to early detection and treatment of at-risk foals (16). In a recently published large scale study, the mortality rate was 23.8%, of which two thirds were euthanized (7). This is similar to the findings in this study of 30.2% (95% CI: 0.21-0.41). In a recent study from Belgium, a foal with sepsis was 1.9 times more likely to die than a foal without sepsis (3), further emphasizing the importance of early recognition and timely referral. This is not statistically significantly different to the results in our study [4.3 (95% CI: 1.2-15.5)].

In our study, attitude, which was defined as normal or abnormal (e.g., hypotonia, coma, depression or seizures), was found to be strongly associated with short term death, within the subset of foals diagnosed as septic. This finding is expected since attitude (hypotonia, coma, depression, convulsions) is part of the sepsis score and provide 1-2 points depending on severity (4). Interestingly, in a previous study on 65 septicemic foals (17) attitude (normal, depressed, moribund, or seizing) was reported for 57 foals, of which 50 were abnormal but no difference was found in the proportion of survivors among foals that had normal versus abnormal attitude. However, the authors concluded that it is possible that a larger study would have resulted in a significant difference (17).

The blood potassium level was also found to be associated with death in foals with sepsis in this study. The risk of death increased with every unit increase in potassium. Although this is the first study to report that an increase in potassium was significantly associated with death in septic foals by multivariable analysis, the median potassium levels of both groups were within normal limits. In human medicine, critically ill patients with abnormal potassium levels (lower or higher than the reference values) had a higher incidence of ventricular arrhythmia and death than patients with normal potassium levels (18). This finding should be evaluated in future research.

Regarding the diagnoses on admission, in a study from Tufts University, foals with omphalitis were more likely to survive, whereas foals with lower respiratory disease or with septic arthritis were more likely to die (8). In Belgium, omphalitis carried a higher risk of death (35%) (3). In this study, of the foals ultimately diagnosed as septic, a foal with sepsis identified on admission was 4.3 times more likely to die than foals with other diagnoses on admission that were significantly associated with death on univariable analysis (Table 5). This finding was unexpected since omphalitis and diarrhea are clinical signs that characterize sepsis. However, in this hospital, there is a routine of performing surgery on foals with omphalitis that are very often foals with diarrhea (19). The improved prognosis of foals with omphalitis on admission, may be a preliminary indication that performing omphalectomies quickly and in large proportions of foals with diarrhea is beneficial.

Limitations: Our study had a number of limitations, primarily, the reliance on retrospective recorded historical and physical examination information, which, on occasion, can be missing data or recorded inaccurately and subjectively (e.g., neutrophil toxicity). The amount of missing data in the medical records may have resulted in omission of pertinent variables while searching for risk factors associating with death among septic foals (e.g., CRT), hence it is not possible to determine that they are not important as well. A further study should be conducted to examine them. Another limitation is that there were many potential risk factors in the univariable analysis, but not enough mortality cases to produce a reliably stable logistic regression model (20). This may have resulted in overfitting. Our study did not rely on blood cultures in the septic foal classification as blood cultures were not routinely examined in this hospital and because a study from 2014 found that positive blood cultures may result from transient bacteremia and may occur also in healthy foals early in the post-natal period (21). This issue may have resulted in misclassification of sick-non-septic foals as septic

foals, or vice versa. Lastly the unique population of foals in this study makes comparisons between studies difficult.

5. Conclusions

In conclusion, we found that our cohort was unique and included mostly Arabian fillies, possibly due to their higher financial value locally. Sepsis was the most common diagnosis, but only half of the foals that were determined as septic in retrospect, by the authors, were diagnosed as such by the clinician on admission. This further demonstrates the need to determine an accepted definition of sepsis in foals.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Systemic Inflammatory Response Syndrome SIRS

Failure of Passive Transfer FPT

Neonatal Maladjustment Syndrome NMS

Confidence Intervals CI

Capillary Refill Time CRT

White blood cell count WBC

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