Journal of Veterinary Internal Medicine
Open Access

J Vet Intern Med 2015;29:659–662

Preliminary Investigation of the Area Under the L-Lactate Concentration–Time Curve (LAC_{AREA}) in Critically Ill Equine Neonates

P.A. Wilkins, B.J. Sheahan, K.A. Vander Werf, C. Castagnetti, J. Hardy, A. Schoster, and R.C. Boston

Background: A variety of measures of L-lactate concentration ([LAC]) in the blood of critically ill neonatal foals have shown utility as prognostic indicators. These measures, evaluating either the severity of hyperlactatemia or the duration of exposure to hyperlactatemia, perform fairly well and have correctly classified 75–80% of foals examined in several studies. The area under the L-lactate concentration versus time curve (LAC_{Area}) encompasses both severity and duration of hyperlactatemia and should improve correct classification of patient survival.

Hypothesis/Objectives: LAC_{Area} is larger in nonsurviving critically ill neonatal foals.

Animals: Forty-nine foals admitted for critical illness to 1 of 4 referral hospitals.

Methods: Whole blood was obtained at admission and 6, 12, 18, and 24 hours after admission for measurement of L-lactate using a handheld lactate meter. LAC_{Area} was calculated for: admission–6, 6–12, 12–18, 18–24 hours, and admission–24 hours using the trapezoidal method and summing the 6-hours interval areas to determine total 24 hours area. Differences between survivors and nonsurvivors were determined using robust regression and Kruskal–Wallis testing, $P < .05$.

Results: LAC_{Area} was significantly larger in nonsurviving foals (n = 9) than in surviving foals (n = 40) at all time periods examined.

Conclusions and Clinical Importance: Differences in LAC_{Area} between surviving and nonsurviving critically ill neonatal foals are large and support further investigation of this method as an improved biomarker for survival in critically ill neonatal foals is indicated.

Key words: Horse; Hyperlactatemia; Intensive care; Lactate clearance; Survival.

Lactate (LAC) is a normal metabolite present in the blood of neonatal foals. Abnormally increased L-lactate concentration is a fairly reliable biomarker of disease severity and outcome in critically ill foals, correctly classifying survival to hospital discharge in approximately 75–80% of cases.[1–5] Increased LAC concentration at admission ($[LAC]_{Admit}$) evaluates the severity or magnitude of initial hyperlactatemia, whereas the change in [LAC] with time ([LAC]Δ) evaluates the duration or persistence of initial hyperlactatemia in the face of treatment. Both, when abnormal, are associated with decreased survival to hospital discharge in ill neonatal foals.[1–5] Although initial hyperlactatemia ($[LAC]_{Admit}$) commonly is caused by poor oxygen delivery to tissues, persistent hyperlactatemia ([LAC]Δ) has been associated with dysmetabolism and poor oxygen utilization by tissues in the face of adequate oxygen delivery.[1,2] This report evaluates the magnitude of the area under the 24-hour [LAC] versus time curve (LAC_{Area}), a unique measure of [LAC] exposure that evaluates both severity and duration of hyperlactatemia, in critically ill neonatal foals. This report also provides a preliminary analysis of differences in LAC_{Area} between surviving and nonsurviving treated foals.

Abbreviations:

LAC	lactate
[LAC]	lactate concentration
$[LAC]_{Admit}$	lactate concentration at admission
[LAC]Δ	lactate concentration change over time
LAC_{Area}	area under [LAC] versus time curve

Materials and Methods

Animals

Neonatal foals <30 days of age presenting to 1 of 4 university or private referral hospitals in 2014 for treatment of conditions requiring intensive or critical care were studied after client informed consent. The study protocol was approved by the University of Illinois Institutional Animal Care and Use Committee (IACUC approval no. 13149).

From the Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois, Urbana, IL (Wilkins, Sheahan, Vander Werf); the Department of Veterinary Medical Sciences, University of Bologna, Bologna, Italy (Castagnetti); the Department of Large Animal Clinical Sciences, College of Veterinary Medicine & Biomedical Sciences, Texas A & M University, College Station, TX (Hardy); the Vetsuisse Faculty, University of Zurich, Zurich, Switzerland (Schoster); and the Department of Clinical Studies, New Bolton Center, University of Pennsylvania School of Veterinary Medicine, Kennett Square, PA (Boston).

Data were collected for this study at the University of Illinois CVM, University of Bologna, Texas A & M CVM, University of Zurich.

The results of this study have not been presented at any scientific meeting as of the time of manuscript submission.

Corresponding author: P.A. Wilkins, Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois, 1008 West Hazelwood Drive, Urbana, IL 1082; e-mail: pawilkin@illinois.edu.

Submitted October 31, 2014; Revised December 13, 2014; Accepted January 20, 2015.

DOI: 10.1111/jvim.12559

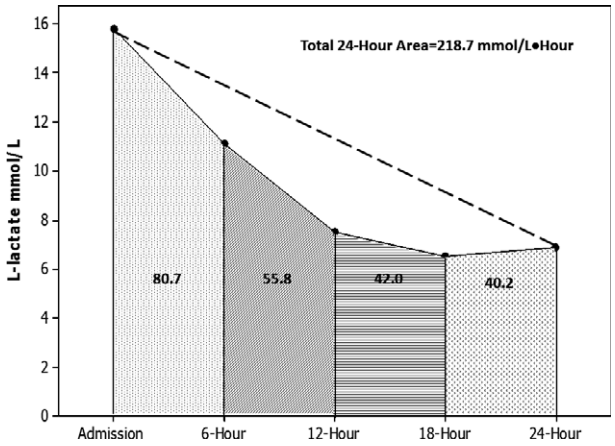

Fig 1. Calculation of L-lactate concentration versus time area under the curve (AUC) using the trapezoid method. The AUC first is calculated for each individual 6 hours interval using the formula for the area of a trapezoid; [½ (h1 + h2)] • b, which becomes for our purposes: [½ ($[LAC]_{Time\,X}$ + $[LAC]_{Time\,Y}$)] • h. Individual AUCs are calculated for each 6-hours interval and then summed to obtain the total AUC for 24 hours. The dashed line represents the top of the total 24-hours AUC calculated using only Admission and 24-hours values, which would have overestimated actual AUC by approximately 25%.

Sampling Protocol

Whole blood (0.5–1 mL) was obtained by either direct venipuncture of a jugular vein using a preheparinized syringe or via aseptically placed IV catheter at admission. Catheter samples were obtained after removing a volume of blood equal to at least 3× the dead space volume of the catheter and associated extension sets. This presample of blood was returned to the patient via the IV catheter. Additional samples were similarly obtained at 6, 12, 18, and 24 hours after the initial sample.

L-Lactate Measurement, Calculation of LAC_{Area}, and Determination of Outcome to Hospital Discharge

[LAC] was determined using the [LAC] measuring techniques currently in use at each participating hospital. LAC_{Area} was determined using samples obtained over the first 24 hours of hospitalization at 6 hours intervals by the trapezoidal method for numerical integration.[6] The trapezoidal method allows for calculation of larger areas under curves by reduction and calculation of smaller areas under the curve. This is accomplished by using the formula for calculating the area of a trapezoid and summing those areas (Fig 1). Short-term outcome was defined as survival or nonsurvival to hospital discharge and was recorded by the participating clinician at each hospital.

Statistical Analysis

Data were tested for normality using the Shapiro–Wilk method. If not normally distributed, data were log transformed. Differences between surviving and nonsurviving foals were tested using Kruskal–Wallis and robust regression methods, $P \leq .05$.

Results

Forty-nine foals were enrolled in the study. The average ± SD age at admission was 36.9 ± 49.4 hours (median 29 hours; range, 0–264 hours). No statistical difference was noted between foals that survived and those that did not. Four foals did not survive the entire 24 hours of initial hospitalization; an additional 5 foals did not survive to hospital discharge. Primary clinical diagnoses determined by the primary attending clinician were: perinatal asphyxia syndrome (11); sepsis (11); diarrhea (8); failure of passive transfer (7); meconium impaction (7); and prematurity, dystocia, flexural deformity, and trauma and premature placental separation ("red bag delivery"), 1 each. Secondary clinical diagnoses included: sepsis (10); failure of passive transfer (10); perinatal asphyxia syndrome (4); flexural deformity (2); and cleft palate, intussusception, trauma, prematurity, diarrhea, and ocular problem, 1 each.

Overall, data were not normally distributed (skewed) and were log transformed for analysis. Lactate concentration at all testing times are presented in Table 1. Briefly, [LAC] were different between foals that lived and those that died at all sampling times except admission. Regarding LAC_{Area}, based on robust regression results, differences between foals that lived and those that died were highly significantly different at all testing periods (Table 2).

Discussion

This study shows that calculation of LAC_{Area} has potential to be a useful indicator of prognosis in critically ill equine neonates, potentially improving ability to predict survival over predictions based on $[LAC]_{Admit}$ or measures of change in [LAC] over time.[1–5,7] Area under the [LAC] versus time curve has been applied to human pediatric patients and shown improvement in both sensitivity and specificity for prediction of outcome when compared to both $[LAC]_{Admit}$ and [LAC]Δ, likely because of its ability to evaluate not only severity of hyperlactatemia but also duration of exposure to hyperlactatemia during the initial therapeutic period.[7] In clinically affected foals, LAC_{Area} is likely to be related to both the persistence and the severity of increased [LAC] during the early course of treatment (ie, it is influenced by the exposure time to hyperlactatemia as well as the actual L-lactate concentrations).

We did not examine increased risk of nonsurvival associated with increased LAC_{Area} because of the relatively low number of nonsurvivors in this study, which precluded statistical analysis. Because of the low number of cases we also did not provide or perform any analysis by primary clinical diagnosis, although this type of analysis would be of interest.

The normal values of LAC_{Area} in equine neonates are now known to be age-dependent and demonstrate significant decreases over the first 3 days of life, with a smaller yet still significant decrease between 3 and 7–14 days after birth.[8] This age-dependent decrease in [LAC] and LAC_{Area} over the first few days of life may confound evaluation of the various LAC measures as tools for evaluating prognosis and disease severity, prematurity also may be an important confounder.[8,9,10] The fetus utilizes L-lactate as an important energy source, and failure

Table 1. L-lactate concentrations obtained at 5 time periods: Admission, and at 6, 12, 18 and 24 hours after admission. Significant differences were identified between foals that lived and those that died at each time period except at admission. Some sampling times were missed for foals surviving for 24 hours; 4 foals did not survive the initial 24 hours of hospitalization and treatment, whereas 5 additional foals did not survive to hospital discharge after the initial 24 hours of hospitalization.

Sample Time	Outcome	Mean ± SD, mmol/L	Median (Range), mmol/L	n	*P* Value
Admission	All	4.9 ± 4.6	3.2 (0.9–21.0)	49	.278
	Lived	4.6 ± 4.1	3.1 (0.9–16.9)	40	
	Died	6.5 ± 6.27	4.1 (1.5–21.0)	9	
6 hours	All	4.8 ± 4.8	2.4 (1.1–22.1)	47	.035
	Lived	4.0 ± 3.8	2.3 (1.1–18.5)	39	
	Died	8.8 ± 73	6.9 (1.7–21.2)	8	
12 hours	All	3.7 ± 3.8	2.3 (1.0–23.0)	47	.028
	Lived	3.1 ± 2.4	2.2 (1.0–11.8)	40	
	Died	7.3 ± 7.2	5.1 (1.4–23.0)	7	
18 hours	All	3.0 ± 2.5	2.1 (0.9–14.6)	43	.035
	Lived	2.8 ± 2.6	2.0 (0.9–14.6)	37	
	Died	4.3 ± 2.2	3.9 (1.6–7.7)	6	
24 hours	All	2.7 ± 2.6	1.9 (0.9–14.8)	45	.010
	Lived	2.4 ± 2.4	1.8 (0.9–14.8)	40	
	Died	5.0 ± 3.0	4.5 (1.8–10)	5	

Table 2. Area under the [LAC] versus time curve calculated using the trapezoid method at 5 time periods: Admission–6, 6–12, 12–18, 18–24 hours, and Admission–24 hours after hospital admission. Significant differences were identified between foals that lived and those that died for all sampling periods. Some sampling times were missed for foals surviving for 24 hours; 4 foals did not survive the initial 24 hours of hospitalization and treatment, whereas 5 additional foals did not survive to hospital discharge after the initial 24 hours of hospitalization.

Sample Time	Outcome	Mean ± SD, mmol/L* h	Median (Range), mmol/L* h	n	*P* Value
Admission–6 hours	All	28.9 ± 26.1	18.3 (7.8–118.7)	47	.017
	Lived	25.8 ± 22.8	18 (7.8–89.4)	39	
	Died	44.1 ± 36.5	32.1 (10.8–118.7)	8	
6–12 hours	All	24.5 ± 22.2	14.6 (7.5–124.8)	46	<.001
	Lived	21.2 ± 16.6	13.8 (7.5–61.5)	39	
	Died	43.1 ± 38.5	33.9 (9.9–124.8)	7	
12–18 hours	All	19.2 ± 14.8	13.2 (5.7–79.2)	43	<.001
	Lived	17.9 ± 14.8	12.6 (5.7–79.2)	37	
	Died	27.1 ± 13.0	27.6 (9.0–47.4)	6	
18–24 hours	All	17.6 ± 15.5	11.6 (5.4–88.2)	42	<.001
	Lived	16.0 ± 15.1	11.4 (5.4–88.2)	37	
	Died	29.7 ± 14.4	26.4 (14.7–53.1)	5	
24 hours Total	All	87.1 ± 67.4	58.5 (27.0–276.0)	42	<.001
	Lived	82.2 ± 62.2	54 (27.0–276.0)	37	
	Died	122.9 ± 44.2	122.4 (61.2–185.7)	5	

to adapt to post-fetal energy metabolism, along with alteration in extravascular volume, may be features of some disease processes.[9,10] Calculation and evaluation of LAC_{Area} in studies of sick equine neonates may require some adjustment for age-related differences; the impact of age differences currently are unknown and were not examined in this study.

In this study, we did not attempt to standardize the method of LAC measurement, which may have increased the variability in the results. We also did not record or consider types or volumes of IV fluids administered which, especially fluids containing dextrose, might have impacted LAC measurement. Finally, participating hospitals were not provided with specific definitions for clinical diagnosis classification. These limitations of the study should be considered when designing future studies to evaluate this potentially useful LAC parameter in ill neonatal foals.

Although survival-to-discharge percentages for critically ill foals have increased to approximately 80% from a low of approximately 50–60% in the 1980s to early 1990s, there remains room for improvement because approximately 20% of all foals evaluated using LAC parameters are currently misclassified regarding

survival to discharge.[1–5] Early identification of foals at greater risk of nonsurvival may be facilitated by use of this easy to calculate, simple, inexpensive stall-side test, allowing for earlier institution of life-saving monitoring, treatment and intervention protocols. A large prospective multicenter study of this potentially useful prognostic indicator is indicated.

Acknowledgments

There was no financial support for this study.

Conflict of Interest Declaration: Authors disclose no conflict of interest.

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

References

1. Borchers A, Wilkins PA, Marsh PM, et al. Admission L-lactate concentration in hospitalized equine neonates: A prospective multicenter study. Equine Vet J 2012;44(Suppl 41):57–63.

2. Borchers A, Wilkins PA, Marsh PM, et al. Sequential L-lactate concentration in hospitalized equine neonates: A prospective multicenter study. Equine Vet J 2013;45(Suppl 45):4–7.

3. Castagnetti C, Pirrone A, Mariella J, Mari JM. Venous blood lactate evaluation in equine neonatal intensive care. Theriogenology 2010;73:343–357.

4. Wotman K, Wilkins PA, Palmer JE, Boston RC. Association of blood lactate concentration and outcome in foals. J Vet Intern Med 2009;23:598–605.

5. Henderson ISF, Franklin RP, Wilkins PA, Boston RC. Association of hyperlactemia with age, diagnosis, and survival in equine neonates. J Vet Emerg Crit Care 2008;18:496–502.

6. Purves RD. Optimum numerical integration methods for estimation of area-under-the-curve (AUC) and area-under-the-moment-curve (AUMC). J Pharmacokinet Biopharm 1992;20:211–226.

7. Young AK, Eun-Ju H, Won KJ, Seong JP. Early blood lactate area as a prognostic marker in pediatric septic shock. Intensive Care Med 2013;39:1818–1823.

8. Sheahan B, Martin V, Po E, Lascola KM, Wilkins PA. L-lactate area in neonatal foals: Preliminary results from birth to 14 days of age. J Vet Emerg Crit Care 2014;24(Suppl 1):S24.

9. Père MC. Materno-fetal exchanges and utilization of nutrients by the fetus: Comparison between species. Reprod Nutr Dev 2003;43:1–15.

10. Pirrone A, Mariella J, Gentilini F, Castagnetti C. Amniotic fluid and blood lactate concentrations in mares and foals in the early postpartum period. Theriogenology 2012;78:1182–1189.

Author/s:
Wilkins, PA; Sheahan, BJ; Vander Werf, KA; Castagnetti, C; Hardy, J; Schoster, A; Boston, RC

Title:
Preliminary investigation of the area under the L-lactate concentration-time curve (LACArea) in critically ill equine neonates.

Date:
2015-03

Citation:
Wilkins, P. A., Sheahan, B. J., Vander Werf, K. A., Castagnetti, C., Hardy, J., Schoster, A. & Boston, R. C. (2015). Preliminary investigation of the area under the L-lactate concentration-time curve (LACArea) in critically ill equine neonates.. J Vet Intern Med, 29 (2), pp.659-662. https://doi.org/10.1111/jvim.12559.

Persistent Link:
http://hdl.handle.net/11343/253111

File Description:
Published version