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Evaluation of a continuous glucose monitoring system in neonatal foals

David Wong[1] | Caitlin Malik[1] | Katarzyna Dembek[2] | Krista Estell[3] | Megan Marchitello[3] | Katie Wilson[1]

[1]Virginia Maryland College of Veterinary Medicine, Virginia Tech, Blacksburg, Virginia

[2]College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina

[3]Marion duPont Scott Equine Medical Center, Virginia Maryland College of Veterinary Medicine, Virginia Tech, Blacksburg, Virginia

Correspondence
David Wong, 205 Duck Pond Drive, Virginia Maryland College of Veterinary Medicine, Virginia Tech, Blacksburg, VA 24060.
Email: dwong@vt.edu

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Ace Construction

Abstract

Background: Monitoring blood glucose concentrations is common in critically ill neonatal foals, especially septic foals and those receiving naso-esophageal feedings or IV parenteral nutrition. Glucose typically is measured using a point-of-care (POC) glucometer but requires repeated restraint and blood collections, which may cause irritation at venipuncture sites and increased demands on nursing staff. Continuous glucose monitoring systems (CGMS) may provide an accurate alternative for monitoring blood glucose concentration.

Objectives: To determine the correlation and accuracy of a CGMS to monitor neonatal foals' blood glucose concentrations as compared to a POC glucometer and laboratory chemistry analysis (CHEM).

Animals: Samples from 4 healthy and 4 ill neonatal foals.

Methods: A CGMS was placed on each foal, and glucose measurements acquired from this device were compared to simultaneous measurements of blood glucose concentration using a POC glucometer and CHEM.

Results: Two-hundred matched glucose measurements were collected from 8 neonatal foals. The mean bias (95% limits of agreement) between CGMS and CHEM, CGMS and POC glucometer, and POC glucometer and CHEM was 3.97 mg/dL (−32.5 to 40.4), 18.2 mg/dL (−28.8 to 65.2), and 22.18 mg/dL (−9.3 to 53.67), respectively. The Pearson's correlation coefficient (r) was significantly correlated among all devices: GCMS and CHEM ($r = 0.81$), CGMS and POC glucometer ($r = 0.77$) and POC glucometer-CHEM ($r = 0.92$).

Conclusions and Clinical Importance: Within the blood glucose concentration ranges in this study (78-212 mg/dL), CGMS measurements were significantly correlated with CHEM, suggesting that it is an acceptable method to provide meaningful, immediate, and continuous glucose concentration measurements in neonatal foals while eliminating the need for repeated restraint and blood collection.

KEYWORDS
critical care, nutrition, point-of-care, sepsis

Abbreviations: CGMS, continuous glucose monitoring system; CHEM, chemistry analyzer; POC, point-of-care.

1 | INTRODUCTION

Derangements in blood glucose concentrations are commonly encountered in critically ill neonatal foals. Hyperglycemia can be caused by altered glucose metabolism, increased hepatic gluconeogenesis, insulin resistance or some combination of these factors.[1] Conversely, hypoglycemia can arise from low endogenous glycogen reserves, inadequate consumption of nutrients, high tissue metabolism in critically ill neonatal foals or a combination thereof.[1-3] In a multi-institutional study, blood glucose concentration was measured in 515 critically ill neonatal foals. In this population, 188 (36.5%) were hyperglycemic (blood glucose concentration >131 mg/dL), 177 (34.4%) were hypoglycemic (<76 mg/dL) and 150 (29.1%) had blood glucose concentrations within normal reference intervals (76-131 mg/dL).[1] Based on the wide variation in blood glucose concentration in ill neonatal foals, a clinically useful device that could accurately monitor blood glucose concentrations within these ranges would be useful.

Blood glucose concentration is routinely measured during the initial diagnostic evaluation of ill neonatal foals. Furthermore, serial blood glucose concentrations are measured (2-6 times/day) in ill hospitalized foals to detect periods of hyper- or hypoglycemia, which have been associated with adverse outcomes and higher mortality rates.[1,4] Additionally, many ill foals receive either supplemental nasoesophageal milk feedings or continuous rate IV infusions of dextrose or other forms of parenteral nutrition, which require frequent monitoring of blood glucose concentration.[5] Blood glucose concentrations typically are measured using a handheld point-of-care (POC) glucometer that requires repeated venipuncture or blood collection from an IV catheter. Either of these techniques requires handling and restraint of the foal, which can result in stress-induced hyperglycemia. Repeated venipuncture also can result in phlebitis or thrombosis and increase owner expense and nursing workload.

Continuous glucose monitoring has been used in the human medical critical care field.[4,6-8] Several continuous glucose monitoring systems (CGMS) have been developed to monitor interstitial glucose concentration primarily for diabetic patients, but also for critically ill people.[4,6,8-10] The CGMS uses a sensor to measure glucose concentration within the interstitial space of the SC tissue by a reaction of glucose with the enzyme glucose oxidase.[11] This reaction converts glucose into gluconic acid and hydrogen peroxide and generates an electric signal proportional to the glucose concentration, which then is converted to a standard unit of measurement (mg/dL).[11] The CGMS devices obtain readings every 5 minutes (totaling 288 readings per day) and are minimally invasive, eliminate the need for frequent blood collection, and facilitate continuous glucose monitoring, thereby aiding in the detection of hypo- or hyperglycemic periods. Studies in people, dogs, cats, and adult horses have yielded favorable results with regard to continuous glucose monitoring, but the single study that investigated the use of CGMS in critically ill neonatal foals produced wide limits of agreement between the CGMS and the standard laboratory assay for measurement of blood glucose.[9,11-13] In 2018, an updated 6th generation CGMS was released (Dexcom G6; Dexcom,

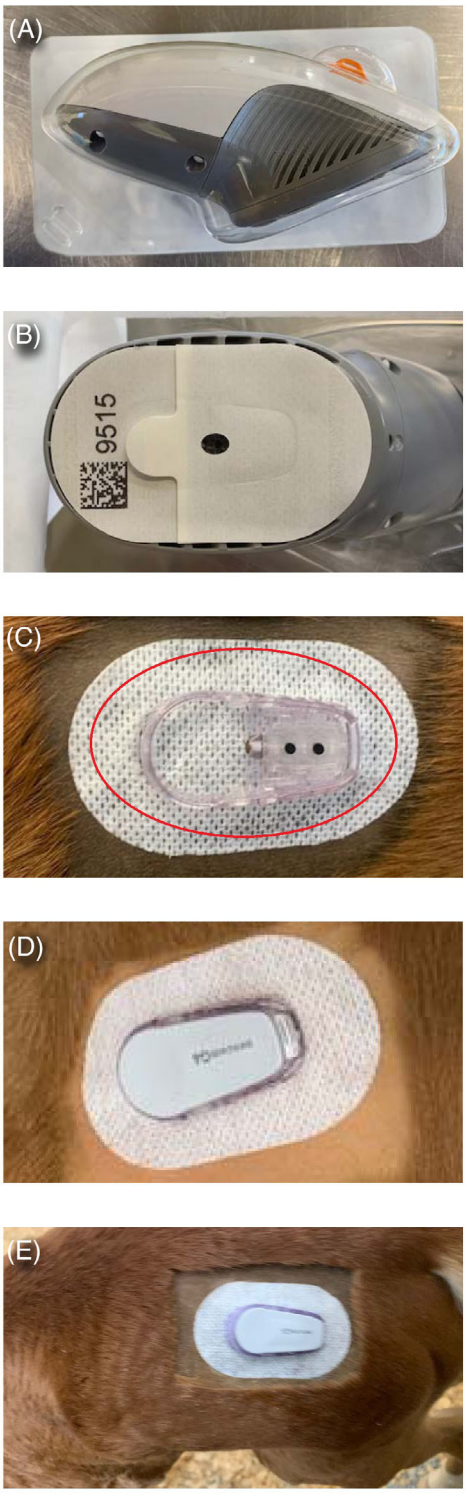

FIGURE 1 Procedure to place CGMS on neonatal foal. A 3-in. × 3-in. area is clipped over the lateral aspect of the hindquarter and cleaned with isopropyl alcohol. A, original packaging of sensor and sensor applicator device; B, bottom of sensor with code needed to register sensor with device reader; labels are removed just prior to insertion to reveal adhesive pad of sensor; C, red oval depicts region where rapid drying adhesive glue is applied to the periphery of the application pad (of note, glue applied on the underside of pad, facing foal's skin); applicator device is then placed firmly on the skin of foal and actuated (D) transmitter is inserted into sensor; E, foal with completed application of CGMS

San Diego, California) with improvements in accuracy of glucose concentration measurement and longevity of use (10 day sensor) in people.[7] If CGMS could accurately measure glucose concentration in neonatal foals, this device could provide real-time glucose results, aid in the monitoring and treatment of ill foals, decrease nursing care, and lessen client expense. The purpose of our study was to evaluate the accuracy of a new generation of CGMS in healthy and ill neonatal foals.

2 | MATERIALS AND METHODS

This study was approved by the university institutional animal care and use committee. Healthy and ill neonatal foals (<14 days of age) evaluated at the Virginia-Maryland College of Veterinary Medicine or the Marion duPont Scott Equine Medical Center were included in the study. Healthy foals were university owned and determined to be healthy based on physical examination findings, CBC, serum biochemistry analysis, and serum IgG concentrations all falling within acceptable reference intervals at ≤24 hours of age. Ill foals were presented for a variety of reasons, with the diagnostic assessment and therapeutic plan left to the discretion of the attending veterinarian. Owner consent was obtained for client-owned foals.

For all foals, a 16-gauge jugular IV catheter was placed using sterile technique to facilitate blood collection (healthy and ill foals) and provide treatment (ill foals). Patency of IV catheters was maintained by irrigation with 6 mL of heparinized saline every 6 hours. A 3-in. × 3-in. area on the dorsal hindquarter was clipped using a #40 clipper blade, cleaned with isopropyl alcohol and a CGMS placed according to the manufacturer's instructions within 24 hours of admission (Figure 1; DexCom G6, DexCom Inc, San Diego, California). To facilitate prolonged placement of the sensor, rapid-drying adhesive glue was placed on the perimeter of the bottom of the sensor pad (Super Glue, Loctite, Westlake, Ohio). The CGMS consists of 3 components: (a) a disposable sensor that has a small transcutaneous fiber that is implanted into the interstitial space upon actuation of the sensor applicator; (b) a transmitter that detects and transmits data; and (c) a handheld wireless reader that receives data using Bluetooth technology and displays glucose concentrations. After application of the sensor and transmitter, a 2-hour calibration period for the CGMS was performed based on manufacturer's instructions.

Upon completion of the calibration period, the glucose concentration measurement from the CGMS was recorded, 5 mL of presample blood and residual heparinized saline was drawn (waste sample) followed by 10 mL of whole blood via the IV catheter. A drop of blood was applied to a POC glucometer (Alpha TRAK2 glucometer, Zoetis Inc, Kalamazoo, Michigan) previously validated for horses[14] and the remainder of the serum sample was submitted to the clinical pathology laboratory for measurement of blood glucose concentration using a standard laboratory chemistry enzymatic method (CHEM). The blood glucose measurement from the laboratory analyzer from the first sample collection was used to calibrate the CGMS (Time 0). Subsequent CGMS readings and blood sample collection and processing for glucose measurements (POC, CHEM) were performed every 6 hours for 6 days.

2.1 | Statistical analysis

Commercial statistics software programs (IBM SPSS Statistics version 24, IBM Corp, NY and Graph Pad Prism version 8, GraphPad Software, California) and statstodo.com were used. Data were tested for normality using a Shapiro-Wilk test and were noted to be normally distributed. Data are presented as mean ± SD. To compare measured glucose concentrations among the laboratory chemistry analyzer (considered the reference standard), POC glucometer, and CGMS, the following paired comparisons were made: POC glucometer-CHEM, CGMS-CHEM, and CGMS-POC glucometer.

Glucose concentrations between 0 and 144 hours were compared among the analyzers using Pearson's linear correlation. Agreement between glucose concentrations for each method of glucose measurement was determined in foals collectively (8 foals) as well as in healthy (4 foals) and ill foals (4 foals) separately, using Bland and Altman and Lin's concordance analyses.[15] Bias was calculated as the mean difference between the POC glucometer and CHEM, CGMS and CHEM, and CGMS and POC glucometer. Positive bias reflected overestimation of glucose concentration as compared to CHEM. Likewise, when comparing the CGMS to POC glucometer, positive bias reflected overestimation of the POC glucometer measurements as compared to CGMS. The limits of agreement were reported as bias ± (1.96 × SD of the bias). Limits of agreement were adjusted based on the method set out by Bland and Altman.[16] The mixed model for

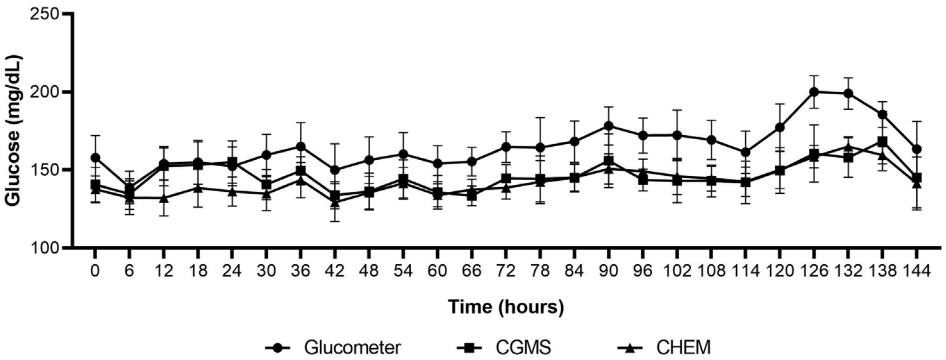

FIGURE 2 Mean ± SD glucose concentrations over 144 hours measured via POC-glucometer, CGMS (Dexcom), and chemistry analyzer (CHEM) in 8 neonatal foals

TABLE 1 Glucose concentration (mg/dL) (0-144 hours) comparisons between the POC glucometer, CGMS (Dexcom), and chemistry analyzer (Chem) in 8 neonatal foals

	Glucometer/Chem	CGMS/Chem	CGMS/Glucometer
Lin's coefficient (95% CI)	0.714 (0.66-0.76)	0.8 (0.74-0.84)	0.67 (0.59-0.73)
Pearson's correlation coefficient (r) (95% CI)	0.92 (0.89-0.93)	0.81 (0.76-0.86)	0.77 (0.7-0.82)
Bland-Altman analysis			
Bias (glucose mg/dL)	22.18	3.97	18.2
95% limits of agreement	−9.3 to 53.67	−32.5 to 40.4	−28.8 to 65.2

2 factors repeated measures analysis of variance (ANOVA) was performed between glucose concentrations obtained by CGMS, POC glucometer and CHEM to assess for the effect of time or assay on glucose concentrations. Tukey's post hoc comparisons were made when relevant. Significance was set at $P \leq .05$. Accuracy also was evaluated simply by the number of CGMS and POC glucometer measurements that were within 10% and 15% of CHEM.[7]

3 | RESULTS

Eight foals were included in the data set. Four foals from the university horse barn were considered healthy, and 4 ill foals were presented for the following primary diseases: sepsis, pneumonia, omphalophlebitis and neonatal encephalopathy. Breeds included Arabian (2), Quarter Horse (1), Thoroughbred (1), Percheron cross (1), Donkey (1), Norwegian Fjord (1), and Mustang (1). The mean age at presentation for healthy and ill foals was 18 and 76 hours, respectively. Application and maintenance of sensors were well tolerated by all foals and upon removal of the sensor, no evidence of irritation or inflammation was noted. A total of 200 sampling times were compared (25 samples/foal). Sensors were left on the 4 ill foals beyond the 6-day study period and used clinically to evaluate glucose concentrations for up to 10 days. Blood glucose concentrations over the study period, measured by CHEM, ranged from 78 to 212 mg/dL: 26 measurements were <100 mg/dL, 117 measurements were between 101 and 150 mg/dL, 55 measurements were between 151-200 mg/dL and 2 measurements were >200 mg/dL. A total of 135/200 (67.5%) of GCMS measurements and 58/200 (29%) of POC glucometer measurements were within 10% of the blood glucose concentration measured by CHEM. In comparison, 170/200 (85%) of GCMS measurements and 99/200 (49.5%) of POC glucometer measurements were within 15% of the blood glucose concentration measured by CHEM.

3.1 | Glucose concentration

No effect of method ($P = .2$) and time points ($P = .33$) on glucose concentrations measured by POC glucometer, GCMS and CHEM was found (Figure 2). Glucose concentrations were significantly correlated with one another (Table 1) among all devices (POC glucometer and CHEM; CGMS and CHEM; CGMS and POC glucometer). The mean

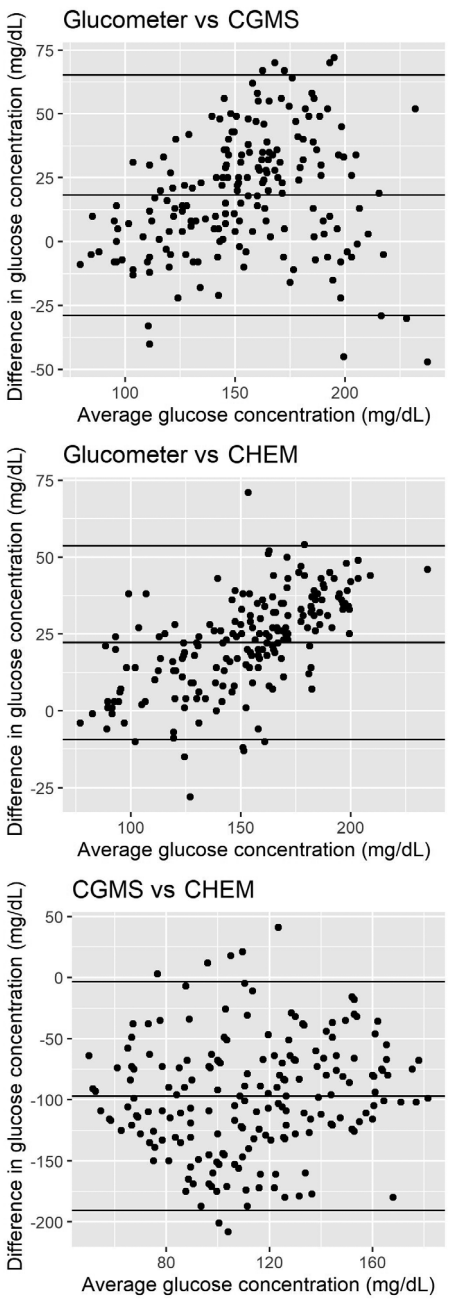

FIGURE 3 Bland-Altman-plots describing the degree of agreement between 2 glucose measuring techniques in 8 neonatal foals. The solid line shows the mean difference, whereas the upper dashed line represents the upper limit of agreement (Diff +1.96 × SD), and the lower dashed line represents the lower limit of agreement (Diff +1.96 × SD)

TABLE 2 Glucose concentration (mg/dL) (0-144 hours) comparisons between the POC glucometer, CGMS (Dexcom), and chemistry analyzer (Chem) in 4 healthy neonatal foals

	Glucometer/Chem	CGMS/Chem	CGMS/Glucometer
Lin's coefficient (95% CI)	0.5 (0.42-0.58)	0.58 (0.48-0.67)	0.52 (0.39-0.63)
Pearson's correlation coefficient (r) (95% CI)	0.9 (0.86-0.93)	0.71 (0.6-0.8)	0.62 (0.48-0.73)
Bland-Altman analysis			
Bias (glucose mg/dL)	23.31	6.2	17.4
95% limits of agreement	−8.2 to 54.8	−35.1 to 47.4	−32.6 to 66.8

TABLE 3 Glucose concentration (mg/dL) (0-144 hours) comparisons between the POC glucometer, CGMS (Dexcom), and chemistry analyzer (Chem) in 4 ill neonatal foals

	Glucometer/Chem	CGMS/Chem	CGMS/Glucometer
Lin's coefficient (95% CI)	0.72 (0.65-0.79)	0.82 (0.74-0.87)	0.62 (0.52-0.7)
Pearson's correlation coefficient (r) (95% CI)	0.9 (0.86-0.94)	0.83 (0.75-0.88)	0.8 (0.72-0.86)
Bland-Altman analysis			
Bias (glucose mg/dL)	20.96	1.6	19.34
95% limits of agreement	−12.5 to 54.4	−29.4 to 32.6	−27 to 65.73

bias (95% limits of agreement) between POC glucometer and CHEM, CGMS and CHEM, and CGMS and POC glucometer for the collective group of 8 foals was 22.18 mg/dL (−9.3 to 53.67), 3.97 mg/dL (−32.5 to 40.4), and 18.2 mg/dL (−28.8 to 65.2), respectively (Figure 3); bias was similar when the foals were divided into healthy and ill foals (Tables 2 and 3).

Lin's concordance correlation coefficient tests how well bivariate pairs of observations conform relative to a gold standard. This test measures both precision and accuracy. The Lin's coefficient between POC glucometer and CHEM, CGMS and CHEM, and CGMS and POC glucometer for the collective group of 8 foals represented moderate to fairly strong agreement according to Altman et al (Table 1).[17] In healthy and ill foals, the Lin's coefficient between POC glucometer and CHEM, CGMS and CHEM, and CGMS and POC glucometer indicated moderate to strong agreement (Tables 2 and 3).[17]

4 | DISCUSSION

In our study, the CGMS was significantly correlated (r = 0.81) with and provided accurate glucose measurements when compared to CHEM in the range of glucose concentrations observed in the study (78-212 mg/dL). This finding is not unexpected because the CGMS was calibrated with CHEM. In our opinion, the mean bias (3.97 mg/dL) between the CGMS and CHEM was within acceptable limits to make clinical decisions in regard to glucose status in the neonatal foal. Although the 95% limits of agreement were somewhat large (−32.5 to 40.4 mg/dL), the fact that 67.5% and 85% of the CGMS measurements were within 10% and 15%, respectively of CHEM supports this view. Similar studies in diabetic people had an overall accuracy of 83.3% (within 15% of blood glucose concentration) when the same CGMS (Dexcom) was evaluated.[7] The POC glucometer also was significantly correlated (r = 0.92) with CHEM measurements, but the mean bias (22.18 mg/dL) indicated that the POC glucometer frequently overestimated blood glucose concentrations in our study. The 95% limits of agreement between the POC glucometer and CHEM were −9.3 to 53.67, but only 29% and 49.5% of POC glucometer measurements were within 10% and 15%, respectively, of CHEM. Therefore, in our study, the CGMS provided more accurate glucose measurements as compared to the POC glucometer.

A previous study in neonatal foals examined an older generation CGMS (Guardian REAL-Time CGMS) and documented a relatively small bias (−1.8 mg/dL), but the 95% limits of agreement were large (−70 to 63.1 mg/dL).[18] Because of the wide limits of agreement, the authors of that study suggested that the usefulness of the CGMS was limited. Presumably, advancements in CGMS technology have improved the accuracy of these devices, as reflected by the results in the foals in our study. Interestingly, the previous study evaluated a different POC glucometer than that used in our study, but noted a mean bias of −2.9 mg/dL between the POC glucometer and CHEM. However, the 95% limits of agreement were large (−32.4 to 27 mg/dL), albeit less than those of the CGMS.[18] The POC glucometer used in our study had a strong positive bias (22.18 mg/dL), with similar 95% limits of agreement as found in the previous study (10.18-35.28 mg/dL). No clinically relevant differences in the CGMS or POC glucometer were noted when individual groups (ill foals, healthy foals) were evaluated (Tables 2 and 3).

A variety of factors could have contributed to the differences in glucose measurement between the devices used in our study. Inaccuracies in glucose measurement have been reported in other studies with possible explanations for the disparity in glucometer performance including hematocrit interference, sample type (whole blood, plasma, venous blood, arterial blood), and analyzer type.[19] In regard to our study, it must be recognized that glucose was measured and

compared among 3 different sample types, namely whole blood (POC glucometer), the interstitium (CGMS) and serum (CHEM). Because of the various sample types and different measuring devices, inherent differences in glucose concentrations and measurements are inevitable. For example, in a study in adult horses, plasma samples were superior to whole blood when using the POC glucometer because the mean difference in glucose concentration measurement between POC glucometry and CHEM using plasma and whole blood was −10.8 and 44.6 mg/dL, respectively.[20] Thus, the various sample types could have contributed to the differences in glucose measurements throughout our study.

Additional studies have compared different methods of measuring glucose. For example, POC glucometry, blood glucose concentration using a blood gas analyzer and CHEM were compared to each other using samples from 19 ill neonatal foals.[21] Correlation was excellent for all comparisons, but the mean difference between concentrations measured using glucometry were 20 mg/dL lower (95% limits of agreement, −51.0 to 10.9) when compared to CHEM and 33 mg/dL lower (95% limits of agreement, 68.6 to 1.5) when compared to the blood gas analyzer.[21] In comparison, the mean difference between concentrations measured using the blood gas analyzer and CHEM was 11 mg/dL higher (95% limits of agreement −15.1 to 37.1). A similar study in adult horses compared a POC glucometer, a blood gas analyzer and CHEM; mean difference between the blood gas analyzer and POC glucometry (plasma sample) was −18.9 (95% confidence interval, −38.9 to 1.1) and −10.8 (95% confidence interval, −36.7 to 15.1) when compared to CHEM, respectively.[21] In our study, we elected to use whole blood samples instead of plasma for POC glucometry, because this sample type is most commonly used in the hospital and field setting. Interestingly, in our study, POC glucometry had a strong positive bias (22.73 mg/dL) as compared to the negative bias noted in other studies.[19,21] Collectively, this information emphasizes the importance of testing each specific glucometer performance and optimal sample type in individual hospitals with blood glucose concentration measured using CHEM before introduction for use in the clinical setting.

Another explanation for discrepancies in glucose measurements that might be observed between the CGMS and CHEM can be attributed to the delay or lag effect between a change in blood glucose and interstitial fluid glucose concentration. In other words, a delay may occur between the relatively instantaneous changes in blood glucose concentration as compared to interstitial glucose concentration. This change, or equilibration, between blood and interstitial glucose concentrations can take up to 5-10 minutes in people.[22] This lag effect can range between 4 and 10 minutes in people using the CGMS (Dexcom G6),[7,22,23] and a delay of 10-60 minutes was detected in a study in adult horses using a different type of glucose monitoring system.[11,24-26] Thus, the clinician should be aware of the fact that CGMS (interstitial) measurements may lag behind blood glucose concentration in situations in which rapid changes in blood glucose concentration occur (eg, IV dextrose bolus, stress-induced hyperglycemia). Another point of interest is that after the first 30 hours of glucose monitoring (Figure 2), the CGMS had subjectively improved correlation with CHEM over time. Similar trends have been noted in people using the DexCom G6 in that the accuracy on the first day of evaluation was 88.6% and 75.4% (within 20% or 15% of gold standard, respectively) as compared to day 10 when the percent accuracy was 90.6% and 80.7%, respectively.[27] Although of limited clinical relevance, accuracy may improve over time.

A moderate amount of cost is associated with use of this specific CGMS. The approximate cost of use includes: Dexcom G6 receiver (reusable, one-time cost) $450 US dollars, transmitter (reusable for 3-4 months) $295, and sensor (1-time use) $135. However, a major benefit of CGMS is its ability to instantaneously measure the patient's interstitial glucose concentration using the device reader, yet it does not require collection of blood from the foal. The sensor was technically easy and feasible to place and, once set, the majority of sensors remained in place for 6 days without complication, with some sensors continuing to provide glucose readings for up to 10 days (data not reported). The additional use of rapid-drying adhesive glue on the sensor likely facilitated maintenance of placement of the sensor. The manufacturer states that the sensors will operate for up to 10 days; thus, these devices may provide valuable information about glucose concentrations in ill foals for prolonged periods of hospitalization. Additionally, these devices allow clinicians to detect trends toward hyper- or hypoglycemia by measuring glucose concentrations every 5 minutes, which allows for tighter glucose surveillance. After calibration, CGMS software allows user-selected high and low glucose concentrations to be set; if the blood glucose concentration goes above or below these preset values, the reader will set off an audible alarm. In addition, users are able to download and digitally display the daily interstitial glucose concentration trends.

Although the accuracy and correlation between the CGMS and CHEM were significant in the range of glucose concentrations in our study, a limitation of the study was that hypoglycemia was not observed in any of the foals evaluated. Thus, we were unable to evaluate the POC glucometer and CGMS in ranges considered to be hypoglycemic (≤75 mg/dL) in neonatal foals. Hypoglycemia was not induced in neonatal foals because, in our opinion, the risk of administering insulin to induce hypoglycemia was outweighed by the potential to induce severe weakness and hypoglycemia, which could be associated with negative complications such as seizures.[28,29] However, in a large study involving 262 diabetic people (children to senior adults) evaluating 21 569 matched paired measurements, the Dexcom G6 provided accurate glucose measurements when blood glucose concentrations ranged from <54 mg/dL to >250 mg/dL.[27] Thus, it is likely that the CGMS would perform within hypoglycemic ranges in foals (reportable glucose range of the device is 40-400 mg/dL), but this supposition will need to be confirmed in future studies of foals because another study in children observed better performance of the Dexcom G6 in the normoglycemic range compared to hypoglycemic measurements.[30]

In summary, the CGMS provided accurate and immediate glucose concentration results within the glucose concentrations observed in our study. Further evaluation is necessary in hypoglycemic neonatal foals, but the CGMS might serve as a method of evaluating glucose concentration in hospitalized ill foals while eliminating the need for repeated blood collection from patients. Importantly, whichever method and sample type the clinician chooses to use for glucose assessment in foals, it is important to use the same method and sample type throughout the

entire treatment period because differences in glucose concentrations among measurement techniques are unavoidable.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the IACUC of Virginia Tech, 19-270.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

David Wong https://orcid.org/0000-0002-6216-0291

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