Safety and Accuracy of Factory-Calibrated Continuous Glucose Monitoring in Pediatric Patients Undergoing Hematopoietic Stem Cell Transplantation

Jenna Sopfe, MD,¹ Tim Vigers, BA,^{2,3} Laura Pyle, PhD,^{2,4}
Roger H. Giller, MD,¹ and Gregory P. Forlenza, MD³

Abstract

Background: Pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) may be at risk for malglycemia and adverse outcomes, including infection, prolonged hospital stays, organ dysfunction, graft-versus-host-disease, delayed hematopoietic recovery, and increased mortality. Continuous glucose monitoring (CGM) may aid in describing and treating malglycemia in this population. However, no studies have demonstrated safety, tolerability, or accuracy of CGM in this uniquely immunocompromised population.

Materials and Methods: A prospective observational study was conducted, using the Abbott Freestyle Libre Pro, in patients aged 2–30 undergoing HSCT at Children’s Hospital Colorado to evaluate continuous glycemia in this population. CGM occurred up to 7 days before and 60 days after HSCT, during hospitalization only. In a secondary analysis of this data, blood glucoses collected during routine HSCT care were compared with CGM values to evaluate accuracy. Adverse events and patient refusal to wear CGM device were monitored to assess safety and tolerability.

Results: Participants ($n = 29$; median age 13.1 years, [interquartile range] [4.7, 16.6] years) wore 84 sensors for an average of 25 [21.5, 30.0] days per participant. Paired serum-sensor values ($n = 893$) demonstrated a mean absolute relative difference of $20\% \pm 14\%$ with Clarke Error Grid analysis showing 99% of pairs in the clinically acceptable Zones (A+B). There were four episodes of self-limited bleeding (4.8% of sensors); no other adverse events occurred. Six patients (20.7%) refused subsequent CGM placements.

Conclusions: CGM use appears safe and feasible although with suboptimal accuracy in the hospitalized pediatric HSCT population. Few adverse events occurred, all of which were low grade.

Keywords: Hematopoietic stem cell transplantation, Pediatrics, Flash glucose monitor, Continuous glucose monitor.

Introduction

GLYCEMIC ABNORMALITIES, including hyperglycemia, hypoglycemia, and glycemic variability, are associated with adverse outcomes in various patient populations, including those with type 1 diabetes (T1D), in intensive care units (ICUs), or undergoing hematopoietic stem cell transplantation (HSCT).^{1–3} In patients undergoing HSCT, in particular, studies have demonstrated associations between

malglycemia (hypoglycemia, hyperglycemia, and/or glycemic variability) and adverse clinical outcomes, including infection, length of hospital stay, organ dysfunction, graft-versus-host-disease, delayed hematopoietic recovery, and mortality.^{3–9} The increased incidence of glycemic abnormalities in these patients has been attributed to a variety of factors, including stress hyperglycemia, underlying insulin resistance, islet damage, steroid treatment, and total parental nutrition administration.³ Increased attention to this problem

¹Department of Pediatrics, Center for Cancer and Blood Disorders, University of Colorado School of Medicine, Aurora, Colorado.

²Department of Biostatistics and Informatics, University of Colorado Denver, Aurora, Colorado.

³Barbara Davis Center, University of Colorado Denver, Aurora, Colorado.

⁴Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado.

and use of developing diabetes technology such as continuous glucose monitoring (CGM) systems may lead to a means to help mitigate adverse outcomes associated with malglycemia.

CGM, including both real-time CGM and flash glucose monitoring (FGM), also known as intermittently scanned CGM, has grown rapidly over the past decade as systems have become more accurate, required fewer calibrations, and been better covered by payers.¹⁰ Several commercially available CGM systems are now factory calibrated, requiring no user input of blood glucose meter data, and labeled for nonadjunctive direct insulin dosing and/or driving of automated insulin delivery.^{11–18}

CGM accuracy continues to be a focus of ongoing development with these devices as successive generations of the technology have shown improved accuracy.^{11–14,18–21} CGM accuracy studies have generally focused on comparison of sensor values against reference laboratory values and clinical evaluation using the Clarke Error Grid (CEG).^{22–24} As sensor accuracy may vary across disease states, it is important to verify CGM accuracy in for new intended uses such as in the pediatric HSCT population, after surgery, or in the ICU.^{20,25–29} In addition, patients undergoing HSCT are severely immunocompromised and may have coagulation deficiencies, which could present additional challenges for CGM use, such as infection or bleeding.

A recent study by our group, of 344 pediatric and adolescent/young adult patients who underwent HSCT at Children's Hospital Colorado, investigated the relationships between glycemic control and HSCT outcomes.³ Glycemic abnormalities were found in 43.9% of patients. Those with a day 0–100 mean glucose of 100–124 mg/dL had a 1.76-fold (95% confidential interval [CI]: 1.10–2.82; $P=0.02$) increased risk of death and those with a mean glucose of ≥ 125 mg/dL had a 7.06-fold (95% CI: 3.84–12.99; $P<0.0001$) increased risk of death compared with patients with a mean glucose <100 mg/dL. These findings, while significant, were obtained by retrospective review of routine laboratory glucose values obtained as part of basic metabolic profiles and other routine testing in this population.

To better characterize the glycemic patterns of these patients, we conducted a prospective observational study of CGM via the Abbott Freestyle Libre Pro (Abbott Diabetes Care, Alameda, CA) in pediatric patients undergoing HSCT. The primary analysis of CGM measured malglycemia and associations between CGM measures and post-HSCT outcomes are being presented in a separate article. In this report, we present a subanalysis of this larger study which focuses on the performance of the CGM in this population, including tolerability and accuracy of the device in the immunocompromised pediatric HSCT population.

Materials and Methods

Subjects

Patients undergoing HSCT at Children's Hospital Colorado were approached for participation in this observational prospective cohort study from February 2017–January 2019. Inclusion criteria were as follows: (1) age 2–30 years at the time of transplant; (2) undergoing HSCT at Children's Hospital Colorado; (3) willing to wear CGM for the duration of the study and willing to follow study protocols. Patients were

excluded for the following: (1) preexisting diagnosis of T1D or type 2 diabetes mellitus (T2D), or insulin requirement in the 2 weeks before transplant; (2) chronic treatment with steroids at the time of HSCT; (3) severe psychiatric disease or developmental delay that may interfere with ability to provide informed consent or wear the CGM; (4) active skin condition that would affect CGM placement; and (5) any other condition that in the opinion of the investigators impaired the person's ability to safely participate in the trial. Participants received a \$50 gift card as appreciation after participating. See Supplementary Material for full protocol. This study was approved by the University of Colorado Institutional Review Board and registered at clinicaltrials.gov (NCT03482154).

Glucose measurement

The Abbott Freestyle Libre Pro (Abbott Diabetes Care) was used to monitor glucose via CGM. The Libre Pro uses the same probe and form factor as the clinical Libre and measures interstitial glucose every 15 min. The Libre Pro is not designed for routine scanning for glycemic assessment, but rather holds up to 14 days of glucose data at a time, which is all downloaded at once upon sensor removal. The Libre has been documented to have a mean absolute relative difference (MARD) of 13.2%.^{18,30} The Libre Pro was selected as this was the only factory-calibrated sensor free from acetaminophen interference on the market at the time this study was initiated.

CGM placement occurred up to 7 days before HSCT, but not before admission to the hospital, any necessary radiotherapy or during and 48 h after thiotepa infusion, as thiotepa has a risk of causing a desquamating rash. Due the immunocompromising nature of HSCT, additional steps beyond standard CGM placement included (1) cleaning placement site with chlorhexidine and (2) use of additional adhesive to avoid early device removal. CGMs were removed at the end of the food and drug administration (FDA)-approved duration of wear (14 days), hospital discharge, and for any computerized tomography, magnetic resonance imaging, or radiotherapy. CGM data were downloaded at each CGM removal and the clinical team was blinded to the data, with the exception of disclosure for extreme values (<50 or >300 mg/dL).

Serum blood glucose values that were measured as part of usual care and their times of draw were extracted from the electronic medical record. Whole-blood glucose values are typically obtained through central venous lines with a 5 mL flush followed by a 3–5 mL blood waste before sample collection. Samples are typically immediately tubed to the hospital's central laboratory, where they are analyzed on a Vitros 5600 machine.

Adverse event monitoring

Adverse event monitoring was performed daily by the clinical team and study nurse. All events were recorded and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.³¹

Statistical analysis

To evaluate CGM accuracy in this study, we determined CGM absolute difference or bias (CGM glucose–serum

glucose) and absolute relative difference ([CGM glucose–serum glucose]/serum glucose), the mean of the latter is termed MARD. Reference serum glucose values were matched against CGM glucose values using the time of the serum blood draw and matching this to the nearest CGM value collected every 15 min. Any positive average difference between CGM and serum was considered positive bias, while any negative difference was considered negative bias, only sensors with no difference between CGM and serum values were considered to have no bias. CEG analysis was performed using the standard ranges defined by Clarke.²³ Variables were assessed for normality using the Kolmogorov–Smirnov test. Continuous variables were compared using *t*-tests or Kruskal–Wallis Rank Sum tests, and chi-squared or Fisher’s exact tests were used for categorical variables. All analyses were performed using R version 3.6.0, and CEG analysis was performed using the ega R package.³²

Results

Patient characteristics

Of the 66 patients meeting study eligibility who were approached for participation, 45.5% consented to participation. A total of 30 patients enrolled in this study; however, 29 patients are included in the analysis as one patient withdrew before wearing a CGM. Patient characteristics are detailed in Table 1. Participants had a median age of 13.1 years (interquartile range [IQR] 4.7, 16.6) and 55% were male. The majority of HSCTs were allogeneic (69%) and the underlying disorder was malignant in 62% of patients. No patients were on insulin therapy during the time of sensor observation. Additional demographic data are available in Table 1.

Sensor accuracy

The Abbott Freestyle Libre Pro CGM values were compared with paired venous laboratory glucose values using the sensor value from the time nearest to the reference value. In total, 893 paired values were included in the accuracy analysis, with a median of 4 min (IQR: 2, 6) between CGM and whole blood glucose values (Table 2). The mean sensor glucose value for these pairs was 95.53 ± 33.71 mg/dL, while the mean venous serum glucose value was 113.83 ± 41.40 mg/dL. The sensor measurements had a mean absolute difference of 24.40 ± 27.05 mg/dL and a MARD of $20\% \pm 14\%$.

Sensor bias was determined for each of the 74 individual sensors with paired laboratory glucose values, with a positive value indicating that the sensor tended to read higher than the venous glucose and a lower value indicating that the sensor tended to read lower than the venous glucose. The median sensor bias was -15.8 mg/dL (IQR: -27.9 , -0.5 mg/dL). The minimum sensor bias was -56.9 mg/dL and the maximum was $+22.5$ mg/dL. Of the 74 sensors, 55 had a negative bias (74.3%), 18 had a positive bias (24.3%), and 1 had essentially no bias (1.4%). Overall, the sensor bias was roughly normally distributed around the median of -15.8 mg/dL (Fig. 1).

CEG analysis of the paired values is displayed in Figure 2. In total, 56.1% of the pairs appear in Zone A, while 42.9% of the pairs appear in Zone B. The clinically acceptable accuracy area of Zone A+Zone B contains 99% of the pairs with 0.8% of pairs in Zone D and 0.2% of the pairs in Zone E. It is notable that the vast majority of pairs ($>99.8\%$) have both a

TABLE 1. DESCRIPTIVE CHARACTERISTICS

Variable	Category	n (%) / median [IQR]
Total cohort		29 (100)
Age at HSCT		13.14 [4.7, 16.6]
Sex	Male	16 (55.2)
	Female	13 (44.8)
Race/ethnicity	Non-Hispanic White	13 (44.8)
	Hispanic	8 (27.6)
	African American	5 (17.2)
	Asian	1 (3.4)
	Multiple	1 (3.4)
	Other	1 (3.4)
Tanner stage	Unknown	0 (0.0)
	1	10 (43.5)
	2	0 (0.0)
	3	2 (8.7)
	4	3 (13.0)
	5	8 (34.8)
BMI percentile	Normal or underweight (<85th percentile)	23 (79.3)
	Overweight (85–95th percentile)	1 (3.4)
	Obese (≥ 95 th percentile)	5 (17.2)
HSCT type	Allogeneic	20 (69.0)
	Autologous	9 (31.0)
Primary diagnosis	Malignant	19 (65.5)
	Nonmalignant	10 (34.5)
Specific diagnosis	Leukemia/MDS	8 (27.6)
	Solid tumors (non-CNS)	7 (24.1)
	Hemoglobinopathy	6 (20.7)
	Lymphoma/lymphoproliferative disease	4 (13.8)
	Bone marrow failure	3 (10.3)
	Primary immunodeficiency/immune dysfunction	1 (3.4)

BMI, body mass index; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MDS, myelodysplastic syndrome.

CGM and serum glucose value of <240 mg/dL. Hypoglycemia was very uncommon via either method ($<1\%$).

Sensor tolerability

The 29 patients wore a total of 84 CGMs, with a median of 2 CGMs per patient [IQR: 2.0, 4.0] and a median of 25 [IQR: 21.5, 30.0] total CGM days (Table 3). Removal of CGM occurred at the maximum wear time of 14 days in 44.6% of CGM wears, whereas the device fell off in 19.3% of CGM wears. Other reasons for removal included discharge

TABLE 2. CONTINUOUS GLUCOSE MONITORING AND BLOOD GLUCOSE MONITORING METRICS

	Mean (SD)
CGM value	95.53 (33.71)
Serum value	113.83 (41.40)
Absolute difference ($n = 893$)	24.40 (27.05)
Absolute relative difference ($n = 893$)	0.20 (0.14)

CGM, continuous glucose monitoring; SD, standard deviation.

FIG. 1. Mean bias by sensor. Bias was calculated for each individual sensor used and the number of sensors with a bias in each range -60 , -50 , -40 , -30 , -20 , -10 , $+10$, $+20$, and $+30$ is shown as a count. The bold red line denotes the area of no bias between the sensor and the reference glucose. Color images are online only.

(20.5%), removal for radiology (6.0%) or radiation (3.6%), patient preference (2.4%), bleeding (2.4%), or removal before thiotepa infusion (1.2%). After initially wearing CGM(s), six participants refused subsequent CGM placement after having worn a range of 2–4 CGMs for a median of 20.0 [IQR: 14.5, 26.25] total days. All six refusals were reported as due to patient preference; notably, four of six of these patients had CGM difficulties such as bleeding (2) or unplanned CGM removal (2) due to need for computed tomography imaging or the sensor falling off.

Four CGM placements were associated with localized, self-limited (Grade 1) bleeding (Table 3), each occurring in a separate participant.³¹ CGMs associated with bleeding corresponded to significantly lower platelet counts compared to CGM placements without bleeding (25.0 vs. 84.0; $P=0.017$). The only other adverse event was bruising. (Table 3).

Discussion

While commercial CGM devices are currently FDA approved for outpatient use in patients with diabetes, there is growing interest in their use in the hospital setting for other conditions at risk for hyperglycemia and other disturbances of glucose metabolism. As such, it is imperative to verify the

FIG. 2. Clarke Error Grid of Abbott Freestyle Libre accuracy in pediatric patients undergoing hematopoietic stem cell transplantation. Points in Zone A indicate the highest agreement between flash glucose monitoring and reference glucose value with Zones B, C, D, and E indicating increasingly worse agreement. Values in Zones A and B are considered clinically acceptable levels of agreement. Color images are online only.

TABLE 3. CONTINUOUS GLUCOSE MONITORING ACCEPTABILITY AND SAFETY

<i>CGM use per patient</i>	<i>Median [IQR]</i>
Number of CGMs	2.0 [2.0, 4.0]
Total days worn	25.0 [21.5, 30.0]
Pre-HSCT	5.6 [2.4]
Post-HSCT	20.0 [15.0, 25.5]
Days worn before sensor fell off/pulled off	8.0 [4.5, 10.0]
Post-HSCT day of last CGM removal	20.0 [15.0, 27.0]
<i>CGM refusal</i>	<i>n (%) / median [IQR]</i>
Patients who refused any CGM placement after the initial wearing	6 (20.7)
Days to CGM refusal	15.0 [9.2, 23.0]
<i>Adverse events per CGM</i>	<i>n (%)</i>
Bleeding	4 (4.8)
Infection	0 (0.0)
Skin reaction	0 (0.0)
Bruising	1 (1.2)
<i>Platelet count for CGM placement</i>	<i>Median [IQR]</i>
All CGMs (with available platelet count) (<i>n</i> = 54)	73.0 [29.5, 180.2]
CGMs with bleeding (<i>n</i> = 4)	25.0 [20.2, 34.0]
CGMs without bleeding (<i>n</i> = 50)	84.0 [32.5, 185.5]

accuracy and usability of these systems in these conditions. Our study indicates that CGM use in the pediatric HSCT population is likely safe and feasible, although the Libre Pro demonstrated a general negative bias, that is, lower CGM glucose determination than venous glucose measurement, with lower than desired accuracy in this population.

Overall, the sensors used during this study have a MARD of $20\% \pm 14\%$ when compared against venous glucose values. Various previous trials have investigated the MARD of the Abbott Freestyle Libre under different conditions. Bailey tested the Libre in 72 subjects with T1D and T2D demonstrating a MARD of 11.4% compared against venous glucose samples.²¹ Fokkert et al. evaluated the Libre in 20 subjects with either T1D or T2D and found an overall MARD of 8.3% (3.5%–13.1%) compared against capillary glucose values.¹⁸ Olafsdottir et al. studied 58 adults with T1D and found a MARD of 13.2% (12.0%–14.4%) compared against capillary glucose values.³⁰ CEG analysis of our data display 99% of pairs in Zone A+B, although only 56.1% in Zone A. Bailey found 99% of values in Zone A+B and 85.5% in Zone A,²¹ while Fokkert et al. found 99.3% of values in Zone A+B and 85.5% in Zone A.¹⁸

The present study displayed worse sensor accuracy than any of the three main comparator studies with a MARD 1.5–2.3 times larger than in those trials. The CEG analysis displays that all the studies found at least 99% of values in Zone A+B, although our study had a much smaller percentage in Zone A than was seen in previous analyses. Clinically, both Zones A and B are acceptable for diabetes management as insulin dosing decisions will generally be safe with values in either of these accuracy areas. However, traditional CGM

assessment focuses on the absolute relative difference under the assumption that the sensor will randomly distribute around the true value. In this study the CEG appears to show a tendency for the sensor to under read relative to the reference values. We thus elected to also evaluate the nonabsolute bias of the sensors to see if the inaccuracy had a directional tendency.

The bias analysis demonstrated that the sensors tended to read about 16 mg/dL below the serum values with a large majority (74.3%) of the sensors displaying some negative bias. This analysis confirms the visual observation of the CEG that there are many points in the lower segment of Zone B. Part of this observation could be due to the fact that this study investigated subjects without known diabetes. As a result, most of the glucose values are <200 mg/dL, where Zone A has a much narrower width for inclusion. For individuals with insulin-dependent diabetes, it may be argued that a negative bias for sensors is somewhat desirable as it would minimize the risk of missing true hypoglycemia, a Zone D or E error, and generally decrease the risk of over-correction, which could also predispose to hypoglycemia. However, when using CGM to assess for mild hyperglycemia, as is the goal in the HSCT population, such a bias would cause underestimation of glycemic stress and thus would be undesirable. It is unknown if negative directional bias is a deliberate “feature” of the Abbott Freestyle Libre, an artifact of the present study, and/or unique to this patient population. We could not identify any prior peer-reviewed literature investigating this topic, and as noted above, other authors have not seen similar Zone B percentages in populations with diabetes. If the negative bias is indeed a design feature for the commercially approved population, future CGM development may require different tuning algorithms depending on the target population.

It is also possible that patient-factors unique to this population could contribute to the worsened sensor accuracy and observed bias. For example, while not reported, increased edema, subclinical bleeding around the sensor probe, or poor interstitial perfusion would negatively impact the observed sensor accuracy. Edema, in particular, would be a factor likely to negatively bias the sensor. Regarding the Zone D points, it is notable that all of these involved significantly elevated serum glucose values compared to euglycemic sensor values. In these hospitalized patients, we suspect that these elevated serum values may be due to contamination of the laboratory sample via drawing off of a glucose-infusing or total parenteral nutrition-infusing line or not performing adequate saline flush and waste per hospital protocol.

Based on this study, CGM use is safe in the pediatric HSCT population, with no occurrence of significant adverse events and most notably, no infections or skin reactions. While 4.7% of CGM placements were associated with bleeding, this was universally mild and self-limited, with no intervention required. As might be expected, CGMs associated with bleeding were also associated with significantly lower platelet counts. While one might consider requiring an increased platelet count before CGM placement, this would use unnecessary resources and risk an adverse transfusion reaction to avoid a very minimal bleeding event, which could be readily controlled by simple local measures.

CGM is not only safe but appears to be acceptable to pediatric HSCT patients and parents as a glucose monitoring option, given this study's consent rate of 46%. We did have a

notable proportion of refusal of CGM placement after several CGM wears (21%), which suggests that CGM was moderately tolerable to our cohort. The majority of these patients had unplanned CGM removals or bleeding events, which may explain lower tolerability in those who refused replacement; some issues might be mitigated in future CGM use, such as by the aforementioned higher platelet requirement before placement. It is worth noting, however, that these patients were not otherwise undergoing fingerstick glucose testing as part of their care and were only wearing CGM for study purposes. If faced with multiple fingersticks per day versus CGM, this technology may have a higher relative tolerance. This study was limited in assessing acceptability due to lack of direct patient feedback, and future studies should use patient-reported measurements of acceptability, particularly in comparison to alternative options, such as fingerstick testing.

The present study has several notable limitations. The protocol was designed to assess correlations between CGM-measured glycemia and HSCT outcomes with assessment of sensor accuracy occurring as a secondary analysis. As such, some parameters which would be collected in a primary sensor accuracy study were not collected. The blood draws were not performed via closed blood sampling devices or with attempt to arterialize the venous samples. Our hypotheses around sources of systematic sensor error such as edema, subclinical bleeding, or poor perfusion are speculative. While the present study was not powered to evaluate these relationships, chart review revealed that four subjects were diagnosed with clinically significant edema, two were diagnosed with mild bleeding, and none was diagnosed with lactic acidosis during the study. Future prospective studies on CGM in acutely ill patient populations may wish to investigate these factors directly. It is also notable that the presence of Zone D and E points on the error grid analysis could be very concerning for patient care. Future accuracy studies would need to evaluate errors of this magnitude in greater detail, including revalidation of the reference measurements.

In patients undergoing HSCT, in particular, studies have demonstrated associations between malglycemia (hypoglycemia, hyperglycemia, and/or glycemic variability) and adverse clinical outcomes, including infection, length of hospital stay, organ dysfunction, graft-versus-host-disease, delayed hematopoietic recovery, and increased mortality.³⁻⁹ CGM use in the pediatric HSCT population may be a way to improve detection of malglycemia, as well as to address it and potentially mitigate associated adverse effects. However, while CGM use in this population appears to be safe and feasible, accuracy was not ideal. Future CGM development targeting nondiabetic populations, in which there is less concern for missing hypoglycemia and therefore negative biasing of the sensor, may be warranted, as well as continued investigation into utility of CGM in this role.

Author Disclosure Statement

G.P.F. conducts research supported by Medtronic, Dexcom, Abbott, Insulet, Tandem, and Lilly; he has served as a speaker, consultant, and/or advisory board member for Medtronic, Dexcom, Abbott, Insulet, Tandem, and Lilly. All other authors report no conflicts of interest pertaining to this work.

Funding Information

This project was supported by research funds from the NIH NIDDK (K12DK094712), the Thrasher Research Fund, and the Cancer League of Colorado.

Supplementary Material

References

1. Nathan DM: The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care* 2014;37:9–16.
2. Brunner R, Adelsmayr G, Herkner H, et al.: Glycemic variability and glucose complexity in critically ill patients: a retrospective analysis of continuous glucose monitoring data. *Crit Care* 2012;16:R175.
3. Sopfe J, Pyle L, Keating AK, et al.: Malglycemia is associated with poor outcomes in pediatric and adolescent hematopoietic stem cell transplant patients. *Blood Adv* 2019;3:350–359.
4. Hammer MJ, Casper C, Gooley TA, et al.: The contribution of malglycemia to mortality among allogeneic hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant* 2009;15:344–351.
5. Storey S, Von Ah D: Impact of malglycemia on clinical outcomes in hospitalized patients with cancer: a review of the literature. *Oncol Nurs Forum* 2012;39:458–465.
6. Derr RL, Hsiao VC, Saudek CD: Antecedent hyperglycemia is associated with an increased risk of neutropenic infections during bone marrow transplantation. *Diabetes Care* 2008;31:1972–1977.
7. Fuji S, Kim SW, Mori S, et al.: Hyperglycemia during the neutropenic period is associated with a poor outcome in patients undergoing myeloablative allogeneic hematopoietic stem cell transplantation. *Transplantation* 2007;84:814–820.
8. Fuji S, Kim SW, Mori S, et al.: Intensive glucose control after allogeneic hematopoietic stem cell transplantation: a retrospective matched-cohort study. *Bone Marrow Transplant* 2009;44:105–111.
9. Garg R, Bhutani H, Alyea E, Pendergrass M: Hyperglycemia and length of stay in patients hospitalized for bone marrow transplantation. *Diabetes Care* 2007;30:993–994.
10. Foster NC, Beck RW, Miller KM, et al.: State of type 1 diabetes management and outcomes from the T1D exchange in 2016–2018. *Diabetes Technol Ther* 2019;21:66–72.
11. Wadwa RP, Laffel LM, Shah VN, Garg SK: Accuracy of a factory-calibrated, real-time continuous glucose monitoring system during 10 days of use in youth and adults with diabetes. *Diabetes Technol Ther* 2018;20:395–402.
12. Slover RH, Tryggestad JB, DiMeglio LA, et al.: Accuracy of a fourth-generation continuous glucose monitoring system in children and adolescents with type 1 diabetes. *Diabetes Technol Ther* 2018;20:576–584.
13. Shah VN, Laffel LM, Wadwa RP, Garg SK: Performance of a factory-calibrated real-time continuous glucose monitoring system utilizing an automated sensor applicator. *Diabetes Technol Ther* 2018;20:428–433.
14. Forlenza GP, Kushner T, Messer LH, et al.: Factory-calibrated continuous glucose monitoring: how and why it works, and the dangers of reuse beyond approved duration of wear. *Diabetes Technol Ther* 2019;21:222–229.

15. Hoss U, Budiman ES: Factory-calibrated continuous glucose sensors: the science behind the technology. *Diabetes Technol Ther* 2017;19(S2):S44–S50.
16. Haak T, Hanaire H, Ajjan R, et al.: Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Ther* 2017;8:55–73.
17. Forlenza GP, Argento NB, Laffel LM: Practical considerations on the use of continuous glucose monitoring in pediatrics and older adults and nonadjunctive use. *Diabetes Technol Ther* 2017;19(S3):S13–S20.
18. Fokkert MJ, van Dijk PR, Edens MA, et al.: Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. *BMJ Open Diabetes Res Care* 2017;5:e000320.
19. Facchinetti A: Continuous glucose monitoring sensors: past, present and future algorithmic challenges. *Sensors (Basel)* 2016;16:2093–2104.
20. Kotzapanagiotou E, Tsotridou E, Volakli E, et al.: Evaluation of continuous flash glucose monitoring in a pediatric ICU setting. *J Clin Monit Comput* 2019 [Epub ahead of print]; DOI: 10.1007/s10877-019-00384-y.
21. Bailey T, Bode BW, Christiansen MP, et al.: The performance and usability of a factory-calibrated flash glucose monitoring system. *Diabetes Technol Ther* 2015;17:787–794.
22. Parkes JL, Slatin SL, Pardo S, et al.: A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. *Diabetes Care* 2000;23:1143–1148.
23. Clarke WL: The original Clarke Error Grid analysis (EGA). *Diabetes Technol Ther* 2005;7:776–779.
24. Klonoff DC, Lias C, Vigersky R, et al.: The surveillance error grid. *J Diabetes Sci Technol* 2014;8:658–672.
25. Forlenza GP, Nathan BM, Moran A, et al.: Accuracy of continuous glucose monitoring in patients after total pancreatectomy with islet autotransplantation. *Diabetes Technol Ther* 2016;18:455–463.
26. Wallia A, Umpierrez GE, Nasraway SA, Klonoff DC: Round table discussion on inpatient use of continuous glucose monitoring at the international hospital diabetes meeting. *J Diabetes Sci Technol* 2016;10:1174–1181.
27. Zhu W, Jiang L, Jiang S, et al.: Real-time continuous glucose monitoring versus conventional glucose monitoring in critically ill patients: a systematic review study protocol. *BMJ Open* 2015;5:e006579.
28. Marics G, Koncz L, Eitler K, et al.: Effects of pH, lactate, hematocrit and potassium level on the accuracy of continuous glucose monitoring (CGM) in pediatric intensive care unit. *Ital J Pediatr* 2015;41:17.
29. Wernerman J, Desai T, Finfer S, et al.: Continuous glucose control in the ICU: report of a 2013 round table meeting. *Crit Care* 2014;18:226.
30. Olafsdottir AF, Attvall S, Sandgren U, et al.: A clinical trial of the accuracy and treatment experience of the flash glucose monitor FreeStyle Libre in adults with type 1 diabetes. *Diabetes Technol Ther* 2017;19:164–172.
31. National Cancer Institute N, DHHS: Common Terminology Criteria for Adverse Events v4.0, v4.0 ed., 2009.
32. ega: Error Grid Analysis. R Package Version 2.0.0. [Computer Program]. Version 2.0.0, 2017.

Address correspondence to:

Jenna Sopfe, MD

Department of Pediatrics

Center for Cancer and Blood Disorders

University of Colorado School of Medicine

13123 E 16th Avenue, B115

Aurora, CO 80045

E-mail: jenna.sopfe@cuanschutz.edu