COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Protocol #: 16-1965
Project Title: Management of diabetic ketoacidosis in children: does early glargine prevent rebound hyperglycemia?

Short Title: "Early glargine in DKA"

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I. Hypotheses and Specific Aims:

Hypothesis 1 (Primary outcome): Early administration of glargine in the treatment of DKA in children will result in reduced rebound hyperglycemia compared to those given standard-of-care management.

Specific Aim 1 (Primary outcome): To evaluate the rate of rebound hyperglycemia (serum glucose level of greater than 180 mg/dL (>10 mmol/L) within 12 hours after discontinuation of IV insulin) in children treated for diabetic ketoacidosis (DKA) with early glargine versus standard-of-care management.

Hypothesis 2: Early administration of glargine in the treatment of DKA in children will result in a reduced rate of recurrent ketogenesis compared to those given standard-of-care management.

Specific Aim 2: To evaluate the rate of recurrent ketogenesis (beta-hydroxybutyrate ≥ 1.5 mmol/L within 12 hours after discontinuation of IV insulin) in children treated for diabetic ketoacidosis (DKA) with early glargine versus standard-of-care management.

Hypothesis 3: The risk of hypoglycemia will not differ between those given early administration of glargine versus those given standard-of-care management:

a. Early administration of glargine in the treatment of DKA in children will not increase hypoglycemic events compared to those given standard-of-care management.
b. Rate of blood glucose decrease while on IV insulin in children with DKA will not be different between those given early administration of glargine versus those given standard-of-care management.
c. Participants who received early glargine will not need more frequent reductions in the IV insulin rate than those given standard-of-care management.

Specific Aim 3: To determine the risk of hypoglycemia between those given early administration of glargine versus those given standard-of-care management.

a. Assess the frequency of hypoglycemic events during treatment of DKA, and within 12 hours after discontinuation of IV insulin, in children given early glargine versus standard-of-care management.
b. Assess the rate of blood glucose decrease while receiving IV insulin in children with DKA given early glargine versus standard-of-care management.
c. Assess the number of participants who needed a decrease in their IV insulin rate between the two groups.

Hypothesis 4 (Exploratory): Continuous glucose monitoring (CGM) will be a feasible and useful tool during DKA treatment in children.

a. CGM will agree with point-of-care (POC) blood glucose levels during DKA treatment in children.

Specific Aim 4 (Exploratory):

a. To evaluate the agreement of CGM and POC glucose monitoring during DKA treatment in children.
b. To determine the percent of CGM failures during DKA treatment in children.
c. To describe the clinical importance of differences between CGM and POC glucose using Clarke error grid analysis.

In summary, this will be a clinical trial with aims to: 1) determine the rate of rebound hyperglycemia in children with DKA given glargine early in the treatment of DKA compared to those given glargine upon complete resolution of the metabolic acidosis (standard-of-care management); 2) evaluate the rate of recurrent ketogenesis in participants given early glargine compared to those given standard-of-care DKA management; 3) assess the risk of hypoglycemia between the two groups; and 4) evaluate the feasibility and utility of CGM as a tool to monitor blood glucose levels during DKA treatment in children.

The importance of this proposal relates to the research and clinical need to establish a smoother transition off of IV insulin in the management of DKA in children and to assess the utility of continuous glucose monitoring during treatment of DKA in children.

II. Background and Significance: *Explain the background of this project so that we will understand why it is important to perform this research project. (Approx. 1 page)*

Type 1 diabetes mellitus (T1D) is one of the leading chronic diseases in childhood with an estimated prevalence of 1:400-500 individuals, and the incidence of type 1 diabetes mellitus is increasing (1,2). Diabetic ketoacidosis (DKA) remains the leading cause of morbidity and mortality in children with T1D (3). The risk of DKA in patients with known T1D is estimated to be 1-10% per patient year, however, those with new onset T1D have been shown to present in DKA in up to 65% of cases (4-6). Further, the rate of new onset T1D patients presenting in DKA increased by 55% from 1998 to 2012 in our center (Children's Hospital Colorado) (7) and the number of hospital visits for DKA nationally increased from roughly 80,000 in 1988 to about 140,000 in 2009 (8). In terms of overall healthcare burden, DKA is responsible for over 500,000 hospital days for adult and pediatric patients resulting in an estimated yearly direct and indirect cost of 2.4 billion USD (9,10).

One frequent complication in DKA associated with in-hospital mortality and longer intensive care stay is hyperglycemia; specifically, rebound hyperglycemia (serum glucose level of greater than 180 mg/dL (>10 mmol/L) within 12-24 hours after discontinuation of IV insulin) (11-13). This outcome has been shown to occur in approximately 40-90% of patients after transition from IV to subcutaneous insulin (11,14,15) and can lead to ketogenesis and recurrence of DKA (16).

Treatment of DKA involves intravenous (IV) fluids and IV insulin to resolve the acidosis, hyperglycemia, and hypovolemia, and frequently requires close monitoring in an intensive care unit. Prolonged treatment with IV insulin not only increases demands on nursing staff, through the need for more frequent blood glucose monitoring, but also increases the risk of hypoglycemia (17). Current guidelines from the American Diabetes Association (ADA), the Joint British Diabetes Societies, and the International Society of Pediatric and Adolescent Diabetes (ISPAD) advise transition to subcutaneous insulin (and discontinuation of IV insulin) once full resolution of ketoacidosis is achieved. However, they include the option to continue a long-acting insulin analog

during the initial management of DKA in patients with established diabetes to reduce the frequency and severity of rebound hyperglycemia and ketogenesis (16-18).

Few studies, primarily in adults, have evaluated the effects of glargine administered early in the management of DKA; however, this has not been well-studied in children. In a retrospective review of 71 children, early administration of glargine in DKA management resulted in shorter duration of IV insulin and shorter acidosis correction time compared to those given standard treatment (19). Another small study showed early glargine reduced average recovery time from DKA without worsening rates of hypoglycemia or hypokalemia (15). Early glargine has also been shown to reduce rates of rebound hyperglycemia in adults with DKA (14,15). However, others have found no difference in length of stay, acidosis correction time, or rate of hypoglycemia in those given early glargine in DKA compared to those given standard treatment (20).

Capillary point-of-care (POC) glucose monitoring is recommended as the preferred method for glucose monitoring in hospitalized patients, however, little has been studied regarding the accuracy and use of interstitial continuous glucose monitoring (CGM, which measures interstitial fluid every 5-10 minutes) in this setting. Using CGM technology may facilitate glycemic control and potentially reduce hypoglycemic events in patients treated with insulin. Limited studies have overall found CGM clinically accurate in both non-ICU and ICU patients including those with hypotension, mild ketosis, edema, and renal failure (21-24). In pediatrics, CGM use has been shown to have good clinical accuracy to POC glucose monitoring in critically ill children and after cardiac surgery (25-27). There currently are no known studies using CGM technology in pediatric patients with DKA.

Overall, given the increasing incidence of T1D in youth, rates of DKA, and hospitalization costs secondary to DKA, a smoother transition to subcutaneous insulin could reduce rebound hyperglycemia, recurrent ketogenesis, and overall hospital length of stay. Further, the use of CGM data will provide novel understanding of the management of DKA in children and of glycemic control after transition to subcutaneous insulin.

III. Preliminary Studies/Progress Report:

Our emergency department sees an average of 150 cases of DKA per year and our center is involved in multiple clinical trials studying DKA management in children. Further, members of our group have been influential in developing a hospital-wide DKA protocol that is utilized both in the emergency department as well as in the inpatient setting to establish standardized and safe clinical care.

Glargine administration early in DKA management has been studied by our colleagues at University of Colorado Hospital in adults (with direct involvement from our co-mentor Cecilia Low-Wang, MD). This group found that early administration of glargine in DKA resulted in a decreased rate of rebound hyperglycemia (33.3% versus 93.5%, $p<0.001$ (14)). This data cannot be directly translated into the care of children in DKA, however, given the increased risk of complications in children such as cerebral edema and adverse events related to severe hypoglycemia. Therefore, without good pediatric data, the timing of glargine administration during the management DKA in children is left up to the discretion of the Diabetes Care Team and is, therefore, variable. Over the past 3-4 years, giving early glargine in DKA in children appears, anecdotally, to work well in the transition to subcutaneous insulin. It is viewed by many Diabetes providers to be a practical method and many are comfortable with this technique.

No data looking exclusively in children exist on whether early glargine administration in DKA management results in reduced rates of rebound hyperglycemia, is protective against recurrent ketogenesis, or how this relates to the risk of hypoglycemia. Further, no data exist on use of CGM technology in children treated for DKA. This detailed information will provide novel knowledge of blood glucose response both during treatment of DKA, and in the immediate phase following resolution of DKA, and help broaden our understanding of type 1 diabetes. CGM use in the hospital may also reduce the risk of hypoglycemic events and therefore improve patient safety.

IV. Research Methods:

A. Outcome Measure(s):

Primary outcome: Rate of rebound hyperglycemia within 12 hours (or until time to hospital discharge if less than 12 hours) after discontinuation of IV insulin on glucometer.

- Percent of patients with blood glucose > 180 mg/dL.
- Median blood glucose.

Secondary outcomes:

1. Rate of rebound hyperglycemia (as described in primary outcome) on CGM.
    - Percent of patients with blood glucose > 180 mg/dL.
    - Median blood glucose.
    - Percent of time with blood glucose > 180 mg/dL.
2. Rate of recurrent ketogenesis (serum beta-hydroxybutyrate ≥ 1.5 mmol/L) within 12 hours (or until time to hospital discharge if less than 12 hours) after discontinuation of IV insulin.
    - Rate of late-recurrent ketogenesis (serum beta-hydroxybutyrate ≥ 1.5 mmol/L) 12-18 hours after discontinuation of IV insulin for participants who remain hospitalized for over 24 hours.
3. Frequency of hypoglycemic events while on IV insulin (and within 12 hours after discontinuation of IV insulin) on glucometer or CGM.
    - Glucometer: percent of patients with blood glucose < 70 mg/dL (+/- 2 hours of an "index" hypoglycemic event).
    - CGM: % of time with blood glucose < 70 mg/dL.
4. Rate of blood glucose decrease while on IV insulin on glucometer and CGM within the following time points: 0-2 hours, 2-4 hours, 4-6 hours, >6 hours.
5. Number of participants who needed a decrease in their IV insulin rate (secondary to hypoglycemia).
6. Feasibility of using CGM as a tool for glucose monitoring in DKA.
    - Percent of CGM failures during treatment of DKA.
    - Correlation of CGM to POC glucose monitoring during DKA.

B. Description of Population to be Enrolled:

Eligible patients will be enrolled from Children's Hospital Colorado Emergency Department; a large tertiary care ED and level I trauma center in Aurora, Colorado. These will be patients with either a known diagnosis of TID presenting in DKA or a new diagnosis of T1D presenting in DKA (see inclusion criteria). Patients will be enrolled either by the PI or a member of the study team (who will be available between the hours of 8:00 am and midnight). Depending on study team member availability, and due to the variability of time of presentation to the ED, patients who present outside of these hours may not be able to be enrolled into the study.

In this study we aim to approach 100 participants, both males and females aged 6-17.99 years, who present in DKA. Assuming 80% of participants approached will be eligible to participate and 60% of eligible subjects will consent to participate, this provides at least 48 subjects, which is needed for 80% power to detect an absolute difference of 40% difference in the rate of rebound hyperglycemia.

Data from adult studies cannot be directly translated into the care of children in DKA given the increased risk of cerebral edema in children and more concern regarding hypoglycemia (both in the hospital and in an ambulatory setting). Therefore, a study looking at the benefits

and safety of giving glargine early in DKA needs to be completed in children and adolescents. We see a large number of patients across the age range of 6 to 18 years who present in DKA and, therefore, expect to obtain a full age distribution in our study participants. Additionally, it is highly possible that younger children respond to DKA management differently than older children and adolescents, therefore, potential sub-analyses within different age groups may need to be utilized.

Inclusion Criteria:
Children meeting the following criteria will be considered for enrollment:

1. Age 6-17.9 years at time of enrollment.
2. Known history of T1D defined as: ≥ 1 positive autoantibody (IAA, GAD, IA-2, or ZnT8), HbA1c ≥ 6.5%, and insulin requirement. Those with a presumed diagnosis of T1D (new onset diagnosis) based on age and presentation will be included in the study and their autoantibody status and HbA1c status will be determined once these results are available. Only those with a diagnosis of T1D (defined above) will be included in the data analysis.
3. Diagnosis of DKA (serum glucose or fingerstick glucose concentration ≥ 200 mg/dL, venous pH ≤7.3 and/or serum bicarbonate concentration ≤15 mmol/L, and presumed ketonemia or ketonuria). Confirmation of ketonemia or ketonuria will be made once these results are available.

Exclusion Criteria:
The following participants will be excluded from the study:

1. Participants who present in DKA with known conditions that affect neurological function such as: suspected alcohol or drug use, severe head trauma, meningitis, etc., that would compromise routine neurological assessment during DKA treatment.
2. Other known complicating illness or poorly-controlled chronic illness that is known to affect blood glucose levels and/or electrolyte balance such as: chronic renal disease (requiring hemodialysis), chronic liver disease (with evidence of current hepatic dysfunction, coagulopathy, and/or chronic hepatitis), or severe chronic lung disease (requiring the use of oral glucocorticoids).
3. Use of medications that are known to affect blood glucose levels (oral glucocorticoids. Metformin, SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, TZDs, sulfonylureas, vasopressors, etc.).
4. Participants who have begun DKA treatment prior to being approached for enrollment and have received more than 6 hours of IV insulin therapy.
5. Participants with established T1D who have received a dose of long-acting insulin within the following time frames:
    a. Tresiba® (Degludec): within the past 20 hours at time of enrollment.
    b. Lantus® (Glargine): within the past 12 hours at time of enrollment.
    c. Levemir® (Detemir): within the past 6 hours at time of enrollment.
6. Participants who are known to be pregnant.
7. Participants who have a known diagnosis of type 2 diabetes (autoantibody negative, use of oral hypoglycemic medications).
8. Participants for whom the treating physicians feel a specific insulin regimen is necessary such that patient safety or well-being could be compromised by enrollment into the study.

C. Study Design and Research Methods

C.1. Recruitment/Enrollment:

Eligible patients will be enrolled from Children's Hospital Colorado Emergency Department after determination of DKA status. Informed consent and assent will be obtained following standard COMIRB approved methods by the PI and/or members of the research team.

Participants completing the informed consent/assent process will be cataloged in a secure (password-protected) database. Data collected will include: Protected Health Information (PHI) including name, date of birth, medical record number, sex, and race/ethnicity. Participants will then be assigned a study number and PHI de-identified.

We have discussed this research protocol with the Emergency Department Research Team and they have determined that this is a suitable study. Further, our department has a long history of collaboration with our Emergency Department.

C.2. Study Protocol:

Participants will be randomized and treated according to the study protocol outlined in Figure 1.

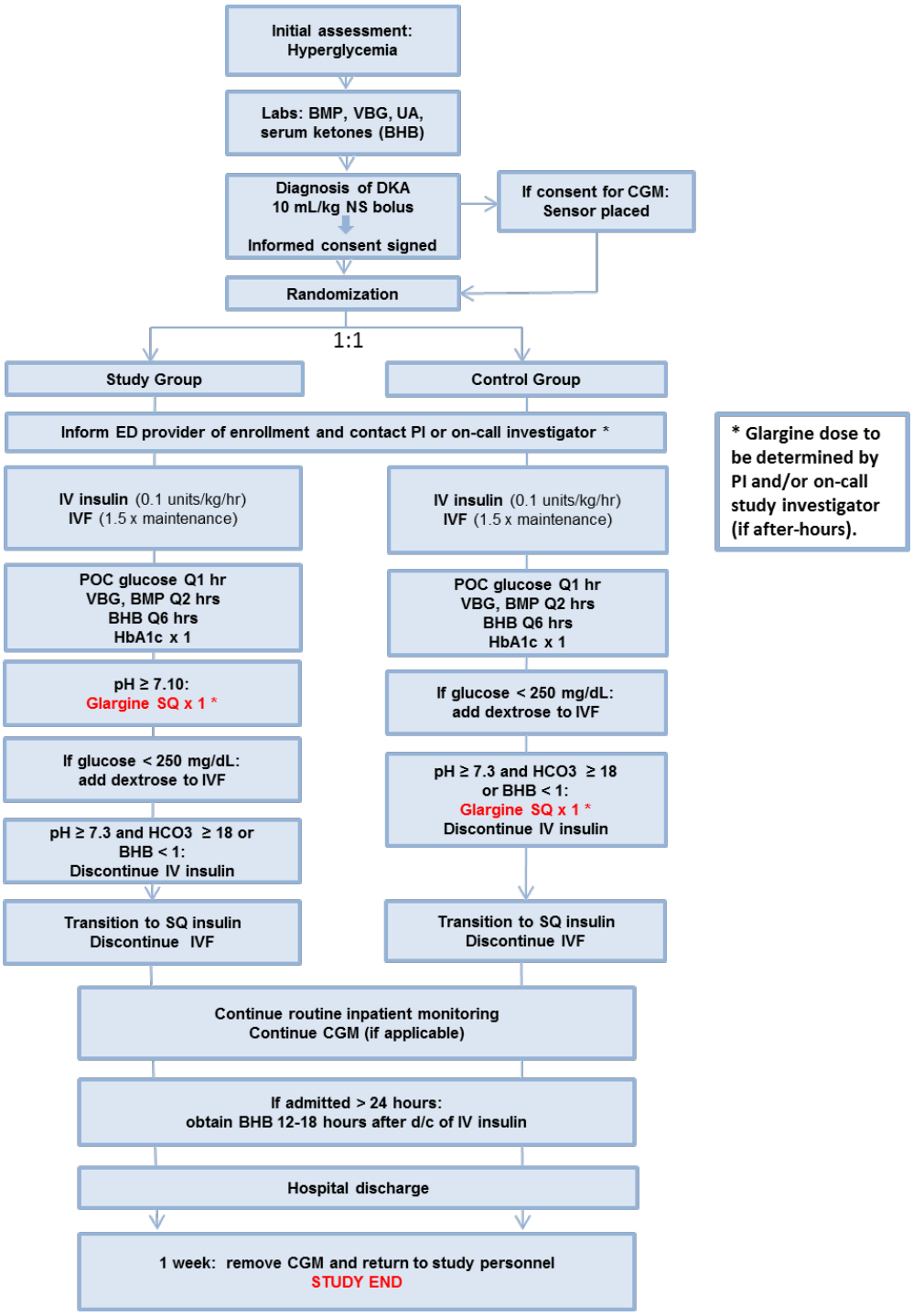

Figure 1: Outline of study protocol. BMP = basic metabolic panel; VBG = venous blood gas; UA = urinalysis; BHB = beta-hydroxybutyrate; DKA = diabetic ketoacidosis; CGM = continuous glucose monitor; NS = normal saline; IV = intravenous; IVF = intravenous fluids; POC = point-of-care; HbA1c = hemoglobin A1c; K = potassium; HCO3 = serum bicarbonate; PI = Primary Investigator.

C. 2.1 During DKA treatment:

- Upon diagnosis of DKA patients will begin rehydration with standard fluid therapy using an initial IV bolus of 10mL/kg of 0.9% saline.
- Fluid boluses may be repeated at the discretion of the treating physician to restore hemodynamic instability.
- During initial therapy, study personnel will obtain informed consent. .
- Participant Data: basic information such as name, date of birth, race/ethnicity, and diagnosis will be collected.
- Randomization:
    - We will use a blocked, stratified randomization scheme to allocate participants 1:1 to treatment groups. Randomization will be stratified within new onset and existing T1D patients to ensure balance across treatment groups.
    - Ideally, randomization will occur during the initial fluid bolus, however, if this is not possible then the patient will be treated with the standard DKA protocol for this study site until consent is completed, but not beyond the time frame outlined in the exclusion criteria.
    - Participants will be randomized into one of two groups:
        1. **Early glargine, study group (N ~ 25):**
            a. Administer glargine SQ x 1 when pH ≥ 7.10.
            b. Primary investigator and/or on-call co-investigator to determine glargine dose:
                i. New onset T1D: 0.3 units/kg
                ii. Established T1D: use home total daily dose (TDD) of long-acting insulin (or TDD of basal if on an insulin pump), converted to glargine equivalents.
        2. **Standard-of-care, control group (N ~ 25):**
            a. Administer glargine SQ x 1 at time of correction of acidosis (venous pH ≥ 7.3 and serum bicarbonate ≥ 18 or BHB ≤ 1) and discontinuation of IV insulin.
            b. Primary investigator and/or on-call co-investigator to determine glargine dose as described above.

- After initial fluid bolus(es), standard insulin therapy begins with a continuous infusion of IV regular insulin at a rate of 0.1 units/kg/hr.
- Ongoing rehydration is established using IV fluids with ¾ normal saline at a standard rate of 1.5 x maintenance unless this is determined to be harmful by the primary attending physician.
- Potassium replacement is provided using IV fluids containing potassium acetate and potassium phosphate.
- When serum glucose concentration declines below 250 mg/dL, dextrose (5-12.5%) is added to the IV fluids to maintain serum glucose between 100 mg/dL and 200 mg/dL.
- If more than 12.5% dextrose IV fluids are needed to maintain serum glucose between 100 mg/dL and 200 mg/dL, the IV insulin rate will be decreased by 0.01 units/kg/hr.

Laboratory Monitoring during DKA treatment:

- Blood glucose concentration is obtained at presentation and hourly while on IV insulin using a point-of-care glucometer or serum measurements.
- Venous pH, serum electrolytes (Na, K, Cl, HCO3, BUN, creatinine) are obtained at presentation and then every 2-4 hours while on IV insulin.
- Serum beta-hydroxybutyrate (BHB) will be obtained at presentation and then every 6 hours while on IV insulin until ≤ 1.0 mmol/L.
- HbA1c will be obtained at presentation.

Continuous Glucose Monitoring (CGM): An option to have CGM sensor placed will be discussed with participant and/or primary guardian. The CGM system used during this study will be the Abbott FreeStyle Libre Pro Flash® Glucose Monitoring System (Figure 2).

Figure 2: Abbott FreeStyle Libre Pro Flash® Glucose Monitoring System:

http://www.freestylelibrepro.us/blood-glucose-monitoring-device.html

The FreeStyle Libre Pro® uses a small low-profile sensor approved for up to 14 days of wear in the USA by the FDA and has shown an average mean absolute relative difference (MARD) of 11.4% over 14 days of continuous wear. The Libre is also marketed as being free from interference with acetaminophen, eliminating this as a concern in our population as this is a common medication used in pediatrics. Further, this system does not require calibration and is blinded from the participant. Data will be available to study personnel at time of download after 1 week of wear.

CGM protocol:

- Following informed consent, an area on the back of the upper arm will be cleaned with an isopropyl alcohol solution and the CGM sensor system will be placed by trained study personnel.
- The CGM sensor placement will ideally occur after initial rehydration has been established, however, if this is not possible the CGM can be placed on the participant at any time during the initial 12 hours of DKA management.
- The CGM sensor will remain on the participant for the duration of hospitalization and an additional week following discharge.
- If a CGM sensor malfunctions during the participant's hospitalization, a new sensor can be replaced by study personnel as soon as possible following knowledge of the malfunction.
- Participants will return the CGM sensor to study personnel after approximately 1 week (see section C.2.3 below).

C.2.2. Upon resolution of DKA:

- When venous pH ≥ 7.3 and serum bicarbonate ≥ 18 mmol/L (or BHB < 1.0 mmol/L) and participant is awake and alert, he/she will be transitioned to subcutaneous insulin:
    - Discontinuation of IV insulin.
    - Initial subcutaneous dosing:

- Glargine: 0.3 units/kg SQ x 1 for new onset T1D (or home glargine equivalent dose for established T1D) – if not already given as part of the Early Glargine/study group (see section C. 2.1 for dosing).
- Lispro: 0.2-0.6 units/kg/day, administered using a standard Multiple Daily Injection (MDI) regimen: before meals or as needed for hyperglycemia (but not more often than every 4 hours).
- The on-call physician can override the above dosing based on clinical judgment.
- **Insulin pump:** Participants with established T1D who are managed with an insulin pump at baseline will have the option to either:
    1. NOT reconnect or use their insulin pump for 24 hours after the protocol glargine dose was administered and will receive standard MDI therapy during that time with dosing determined by the inpatient diabetes team or study personnel. They can resume full home insulin pump use after 24 hours following glargine administration.
    2. Reconnect their home insulin pump to use for BOLUSING ONLY with meals and snacks and will not use their basal rate (set a temporary basal rate of 0%) for 24 hours after the glargine dose was administered. They can resume full home insulin pump use after 24 hours following glargine administration.

Laboratory monitoring upon resolution of DKA:

- Blood glucose concentration obtained before meals, at bedtime, and at 0200 using point-of-care glucometer.
- Serum BHB obtained every 6 hours until ≤ 1.0 mmol/L or at any time if blood glucose on glucometer is > 300 mg/dL for two consecutive measurements.
- Participants who remain hospitalized over 24 hours will have a BHB drawn at 12-18 hours after discontinuation of IV insulin to assess for late-recurrent ketosis.

Table 1: Summary of laboratory monitoring:

Data:	During DKA	Upon resolution of DKA
POC glucose (mg/dL)	At presentation and hourly	Before meals, at bedtime, at 0200
BMP	At presentation and approx. every 2-4 hours	As needed
HbA1c (%)	At presentation	
VBG	At presentation and approx. every 2-4 hours	As needed
BHB (mmol/L)	At presentation and every 6 hours until ≤ 1.0	12-18 hours after d/c of IV insulin* As needed for POC glucose > 300 x 2
UA	At presentation	If POC glucose > 300 mg/dL x 2
CGM	Placed at time of enrollment	Wear x 1 week

BMP = basic metabolic panel; VBG = venous blood gas; BHB = beta-hydroxybutyrate; DKA = diabetic ketoacidosis; CGM = continuous glucose monitor; IV = intravenous; POC = point-of-care; HbA1c = hemoglobin A1c; * for those participants who remain hospitalized after 24 hours.

C.2.3. For participants who consented to wear a CGM (if study funding allows):

- New onset participants: the CGM sensor will be removed either by the participant/family or if needed by clinical staff at the routine 1 week follow-up visit at the Barbara Davis Center (BDC). The device will then be returned to the study team for data download.
- Established participants with type 1 diabetes: these participants will be provided with supplies to mail the CGM to study personnel at the Barbara Davis Center after wearing it for 1 week or will have the option to return the CGM to the BDC in person in 1 week.
- If the CGM sensor malfunctions or becomes disconnected after discharge from the hospital prior to the 1 week time frame the participant will be asked to return the CGM to study personnel at the Barbara Davis Center for data download either by mail (see above) or at their routine 1 week follow-up visit.

C.3. Funding: We have secured small study funds through the Children's Diabetes Foundation (Barbara Davis Center) to cover the cost of the CGMs and Research Assistant (recruitment and consenting) compensation. However, this protocol can be implemented without funding if needed as the essential components (primary outcomes) are not dependent on funding. The laboratory testing required to assess our primary outcomes falls under standard-of-care management for DKA. Further, wearing a CGM is an optional part of the study and many of our secondary outcomes can be assessed without CGM use if needed. Further, departmental funds through the Barbara Davis Center will be available to cover small unanticipated costs.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Participant Data: In order to investigate our primary and secondary outcomes we will collect the following Protected Health Information (PHI) from the study participant:

- Standard medical history, name, date of birth, race, and diagnosis.
- Lab collection: serum glucose, serum bicarbonate, serum sodium, serum chloride, serum potassium, serum blood urea nitrogen, serum creatinine, and serum beta-hydroxybutyrate will obtained using standard venipuncture methods per hospital policy by trained staff. These measurements will be determined using standard methods in the Children's Hospital Colorado core laboratory. Blood glucose and beta-hydroxybutyrate will also be obtained using a point-of-care meter per hospital policy or at the Barbara Davis Center.

DKA protocol: Aside from the timing of glargine administration, all other treatment of DKA will be per the standard hospital DKA protocol (clinical care guidelines) at Children's Hospital Colorado. Available at: https://ccguidelinesportal.childrenscolorado.org/guidelines/

Glargine administration: This is a long-acting insulin analog which could theoretically increase the risk of hypoglycemia during its duration-of-action (20-24 hours). However, this is standard therapy for type 1 diabetes management with a long history of safe use. As such, study participants will receive glargine regardless of which study group they are randomized to; the only difference being the timing of glargine administration. Further, one of our secondary outcomes is to determine the risk of hypoglycemia between those given glargine early in DKA management versus those given glargine at time of DKA resolution.

CGM data collection: Wearing a CGM will be optional for study participants and included in the protocol as funding allows. The CGM sensor will be placed by trained study personnel to reduce risk of injury and/or sensor malfunction and to improve compliance. The CGM data will be downloaded after 1 week using standard industry software by trained staff or study personnel and the information stored in a locked study office.

Plan to minimize risk:

1. Participant Data: Collection of patient data always holds a small risk of data breech. All research staff will be trained in good clinical practice and HIPAA. Any paper PHI will be stored in a locked study office and all electronic data records maintained by the study investigator for analysis will be password protected. Participants will be assigned a study number and de-identified datasets using only the study number will be used for analysis. This study number will be linked to the participant's PHI through a table accessible only to the PI, co-investigators, and research staff. Any other electronic or paper records which could be linked to the participant record or medical chart will be deleted or destroyed. PHI will not be connected to the data used in any manuscript or publication.

2. General: An experienced Diabetes Team (Barbara Davis Center) is routinely consulted on all patients with type 1 diabetes who present to Children's Hospital Colorado and is closely involved in their care throughout the hospitalization with regard to DKA management, blood glucose monitoring, and subcutaneous insulin dosing. The primary Diabetes Team routinely dictates when glargine is administered and at what dose. See "Subcutaneous insulin injection" section for additional details.

3. Hypoglycemia: blood glucose levels will be monitored closely throughout the hospitalization and hypoglycemic events will be treated per standard hospital hypoglycemia protocol. It is routine to monitor blood glucose hourly while on IV insulin and at least 4 times per day once off IV insulin. Once discharged from the hospital, participants will be instructed to check blood glucose levels at least 4 times per day and to call the Barbara Davis Center with any hypoglycemia issues or concerns.

4. Venipuncture to draw blood for laboratory evaluation: Venipuncture will be performed by clinical staff with experience with venipuncture to reduce the risk of pain and/or infection. Gloves will be worn and the area of skin cleaned per hospital policy to prevent risk of infection.

5. Subcutaneous insulin injection: Insulin will be administered subcutaneously during the hospitalization by trained clinical staff with experience in subcutaneous medication dosing. Further, the dose of subcutaneous insulin will be determined by the primary Diabetes Team and/or the PI. Once discharged from the hospital, the participant will be told to contact the Barbara Davis Center with any issues or concerns at home.

6. CGM: Wearing a CGM will be optional to study participants. Additionally, the CGM sensor will be placed by trained study personnel to reduce risk of injury and/or sensor malfunction and to improve compliance. The area where the sensor is to be placed will be cleaned with an isopropyl alcohol solution prior to placement to reduce any risk of infection at the site.

V. Adverse Event Reporting:

Adverse events and/or unanticipated problems will be recorded in a log for tracking purposes. Unanticipated problems will be reported to the IRB within 10 business days of knowledge of the

event. Severe or serious adverse events will be reported to the IRB immediately. Adverse events include:

1. Severe hypoglycemia (blood glucose < 70 mg/dL resulting in seizure, need for glucagon injection, or need for IV dextrose bolus).
2. Cerebral edema (requiring treatment with IV mannitol or IV 3% hypertonic saline).
3. Recurrent ketogenesis (serum beta-hydroxybutyrate > 2.0 mmol/L after discontinuation of IV insulin).
4. Infection or allergic reaction at CGM insertion site.

Criteria to pause or stop the study protocol:
Study protocol will be halted or stopped if:

- Patients in the study group experience a disproportionate number of severe hypoglycemic events than those in the control group.
- Patients in the study group experience a disproportionate number of cerebral edema events than those in the control group.
- A significant number of patients (greater than 30 %) develop skin infections at the CGM site requiring antibiotic treatment.
- Participants in the control group experience a disproportionate number of recurrent DKA events requiring treatment with IV insulin after initial resolution.

VI. Potential Scientific Problems:

In any clinical study unforeseen human factors provide challenges. This current study is based on a previous study in adults (14) with no reported adverse events such as increased hypoglycemia in those given glargine early in DKA management. However, the primary physician or Diabetes Team may decide to change the participant's DKA management plan and they would, therefore, come off the study protocol. Additionally, the accuracy of a CGM (which samples interstitial fluid) when used in states of dehydration has not been well-studied. However, a number of small studies have shown CGM to be an accurate measure of blood glucose in an ICU setting (21,25). To improve CGM accuracy we will place the CGM only after initial intravascular hydration has been completed and the CGM will be calibrated (if needed) using a POC glucometer at least twice daily. Additionally, we will continue to obtain frequent POC glucometer readings throughout the hospitalization as this will be used to measure our primary outcome.

We have also performed careful power calculations to allow meaningful analyses of our data.

VII. Data Analysis Plan:

Table 1: Power calculations:

Significance level	0.05	0.05	0.05	0.05	0.05
Effect size (%)	20	25	30	40	50
Odds Ratio	2.333	2.852	3.500	5.444	9.333
Power (%)	80	80	80	80	80
Total N	186	122	84	48	30

Per our power analysis (Table 1), with a total sample size of 48-50 (24-25 per group) we will have 80% power to detect an absolute difference of 40% in rebound hyperglycemia between the two study groups. These power analyses assume that 30% of participants in the early glargine group will experience rebound hyperglycemia. Chi-squared tests will be employed to evaluate whether the difference in rebound hyperglycemia between the two study groups is statistically significant. We will also use logistic regression to adjust for potential confounders (*BMI, sex, age, established T1D versus newly-diagnosed T1D)*. Using a blocked and stratified randomization plan we expect to have similar numbers of newly-diagnosed T1D and known T1D patients in each group.

The data collected by CGM will be summarized for each patient and day into variables describing glycemia, such as mean glucose, area under the curve, area under the curve >180 mg/dL, and percent of time spent above or below particular glucose thresholds (e.g., >180, <60, and <70 mg/dL). Trends over time in these summary statistics will be evaluated graphically to give insight into blood glucose response during treatment of DKA and immediately after resolution of DKA. For variables without an excess of zero values, we will use linear mixed-effects models to compare trajectories over time in the two groups. We will also calculate the mean value of each of these statistics for each patient and compare the groups using t-tests or nonparametric equivalent. Bland-Altman plots will be used to evaluate the agreement between CGM glucose variables (e.g., mean glucose) and POC glucose. To interpret the clinical relevance relevance of any discrepancies between the two sets of measures, we will use Clarke error grid analysis, which classifies pairs of blood glucose measurements made by two methods into categories based on the impact the discrepancy would have on treatment decisions.

VIII. Summarize knowledge to be gained:

Limited data suggest that administration of glargine early in DKA management may reduce rebound hyperglycemia, recurrent ketogenesis, and overall hospital length of stay; however, this has not been well-studied in children. Given the increasing incidence of T1D in youth, frequency of DKA, and hospitalizations secondary to DKA, a smoother transition to subcutaneous insulin could reduce in-hospital morbidity and overall cost per admission. Therefore, we propose to evaluate the effects of early glargine in pediatric DKA management. Additionally, there currently are no known studies using CGM technology in DKA in children evaluating rebound hyperglycemia and the transition to subcutaneous insulin. Therefore, these data will be vital in assessing our primary and secondary outcomes and in broadening our understanding of DKA management in this population.

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