JPPT | Single-Center Retrospective Study

Evaluation of Early Insulin Glargine Administration in the Treatment of Pediatric Diabetic Ketoacidosis

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OBJECTIVE In the management of diabetic ketoacidosis (DKA), the standard of care is to administer insulin glargine after ketoacidosis has resolved and the patient is transitioning from intravenous (IV) insulin to subcutaneous insulin; however, there is evidence to suggest that earlier administration of insulin glargine may accelerate resolution of ketoacidosis. The objective of this research is to determine the efficacy of early subcutaneous insulin glargine on time to resolution of ketoacidosis in children with moderate to severe DKA.

METHODS This retrospective chart review evaluated children age 2 to 21 years old admitted for moderate to severe DKA who received insulin glargine within 6 hours of hospital admission (early insulin glargine) compared with those who received insulin glargine greater than 6 hours from admission (late insulin glargine). The primary outcome was duration of time the patient received IV insulin.

RESULTS A total of 190 patients were included. The median time on IV insulin was lower in patients who received early insulin glargine compared with those who received late insulin glargine (17.0 [IQR, 14–22.8] vs 22.9 hours [IQR, 4.3–29.3]; p = 0.0006). Resolution of DKA was faster in patients who received early insulin glargine compared with those who received late insulin glargine (median, 13.0 [IQR, 9.8–16.8] vs 18.2 hours [IQR, 12.5–27.6]; p = 0.005). Length of pediatric intensive care unit (PICU) and hospital stay and incidences of hypoglycemia and hypokalemia were similar between the 2 groups.

CONCLUSIONS Children with moderate to severe DKA who received early insulin glargine had a significantly lower time on IV insulin, as well as significantly faster time to resolution of DKA when compared with those who received late insulin glargine. There were no significant differences observed in hospital stay and rates of hypoglycemia and hypokalemia.

ABBREVIATIONS BG, blood glucose; DKA, diabetic ketoacidosis; IV, intravenous; PICU, pediatric intensive care unit; POC, point-of-care; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

KEYWORDS basal insulin; diabetic ketoacidosis; long-acting insulin; pediatrics

J Pediatr Pharmacol Ther 2023;28(2):149–155

DOI: 10.5863/1551-6776-28.2.149

Introduction

Diabetic ketoacidosis (DKA) is a condition that resulted in 188,965 hospitalizations in the United States in 2014, with 11% of the admissions being children younger than 17 years of age.[1] Diabetic ketoacidosis is the leading cause of mortality in children with type 1 diabetes mellitus (T1DM) at a rate of 0.15% to 0.30%.[2] Diabetic ketoacidosis is a result of insulin deficiency and an increase in counterregulatory hormones. This imbalance results in hyperglycemia, hyperosmolarity, ketosis, and acidosis. The appropriate management of DKA is necessary to avoid complications associated with hypoglycemia and hypokalemia, such as cerebral edema and cardiopulmonary and neuromuscular compromise.[1,2] Time on intravenous (IV) insulin may increase risk of morbidity and mortality associated with the treatment of DKA, resulting in a need to explore strategies to shorten the time an individual requires treatment with IV insulin.[2]

According to the International Society for Pediatric and Adolescent Diabetes, the standard of care for pediatric DKA includes beginning IV insulin at 0.05 to 0.1 unit/kg/hr at least 1 hour after starting fluid replacement therapy.[2] These guidelines suggest that there may be benefits to the administration of insulin glargine while a patient is receiving IV insulin.[2] Concomitant administration of insulin glargine with IV insulin has been shown to accelerate resolution of ketoacidosis and prevent rebound hyperglycemia in pediatric patients and adults.[3–5] Although the guidelines suggest there is benefit to insulin glargine administration while on IV insulin in the management of DKA, it is not the standard of care due to limited evidence.

The objective of this study is to build upon the limited existing data to determine if early initiation of subcutaneous insulin glargine, along with IV insulin, improves

Table 1. Contents of Initial Fluids

	Bag 1	Bag 2
Dextrose %	D10	—
NaCl Concentration*	NS	NS
Electrolytes	Dependent upon initial serum potassium concentration: • Potassium > 5.5 mEq/L: No fluids with potassium • Potassium < 5.5 mEq/L and <35 kg: 20 mEq/L KCl and 13.6 mmol/L KPhos for a total of 40 mEq/K/L • Potassium < 5.5 mEq/L and ≥ 35 kg: 40 mEq/L KCl and 13.6 mmol/L KPhos for a total of 60 mEq/K/L	
Rate	Dependent upon POC BG: • If POC BG > 300 mg/dL: 0 × mIVF • If POC BG 150–300 mg/dL: 0.75 × mIVF • If POC BG <150 mg/dL: 1.5 × mIVF	Dependent upon POC BG: • If POC BG >300 mg/dL: 1.5 × mIVF • If POC BG 150–300 mg/dL: 0.75 × mIVF • If POC BG < 150 mg/dL: 0 × mIVF

BG, blood glucose; KCl, potassium chloride; KPhos, potassium phosphate; mIVF, maintenance IV fluid rate; NaCl, sodium chloride; NS, sodium chloride 0.9%; ½ NS, sodium chloride 0.45%; POC, point of care

* Prescribers could use ½ NS in patients with hyperchloremic acidosis.

pediatric DKA treatment outcomes without increasing the risk of adverse effects. The primary outcome of this study was the duration of time the patient received IV insulin in hours. Secondary outcomes included length of pediatric intensive care unit (PICU) and hospital stay, time to resolution of DKA in hours, total units of IV insulin infused, average rate of blood glucose decline while on IV insulin, and the incidence of hypoglycemia and hypokalemia.

Materials and Methods

This was a retrospective cohort study of patients [2] to 21 years old admitted to the University of New Mexico Children's Hospital PICU for DKA from July 2014 to September 2020. Patients with moderate or severe DKA who received insulin glargine while on IV insulin were included in data collection and analysis. Moderate DKA was defined as pH 7.11 to 7.2 or serum CO_2 6 to 10 mmol/L; severe DKA was defined as pH < 7.1, serum CO_2 < 5 mmol/L, or mental status changes.2 Patients with mild DKA, patients who received systemic steroids during the hospital admission, and patients who had another etiology of ketosis besides new-onset or existing T1DM, or with known type 2 diabetes mellitus (T2DM) were excluded.

Data were collected from an electronic health record and stored in a manner that de-identified the data. Baseline data collected included age, weight, existing diagnosis of T1DM or new-onset T1DM, severity of DKA upon hospital admission, home dose of long-acting insulin for those with existing T1DM, dose of insulin glargine administered in the hospital, and time from admission to the first dose of insulin glargine. Short-acting insulin doses prior to admission were not collected because it was suspected that most would be sliding scale insulin and it was determined by the authors that this baseline variable would not be directly applicable to this study. Baseline laboratory values collected included serum creatinine, blood urea nitrogen, potassium, hemoglobin A1c, serum bicarbonate, and pH. Other laboratory data collected were lowest blood glucose while on IV insulin and lowest potassium while on IV insulin.

The patients were divided into 2 groups based on if they received insulin glargine within 6 hours of admission (early insulin glargine) or insulin glargine greater than 6 hours from admission (late insulin glargine). Those who received insulin glargine at an outside hospital or en route to the hospital (n = 5) were included in early insulin glargine group.

Time to resolution of DKA was defined as the time in hours to a pH > 7.3 and serum bicarbonate > 15 mmol/L. Incidence of hypoglycemia was defined as the number of patients who had a blood glucose < 60 mg/dL while on IV insulin. Incidence of hypokalemia was defined as the number of patients that had a serum potassium < 3.5 mEq/L while on IV insulin.

All patients were treated according to the institution's standard DKA treatment guideline. Patients received initial fluid resuscitation with normal saline 10 to 20 mL/kg (maximum 1000 mL) bolus, followed by IV fluids at a 1.5 to 2 times maintenance rate (calculated using the Holliday-Segar method) via a 2-bag system (Table 1). The first bag (bag 1) contained dextrose 10%, sodium chloride, and electrolytes. The second bag (bag 2) contained only sodium chloride and electrolytes. Although the preferred fluids per our institution guideline contain normal saline, the providers had the option to use ½ normal saline in patients with hyperchloremic acidosis. Fluid rates were titrated based on hourly point-of-care (POC) blood glucose (BG) readings to increase or decrease the glucose infusion rate to avoid rapid fluctuations in blood glucoses (Table 1). The standard

Table 2. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Early Insulin Glargine (n = 58)	Late Insulin Glargine (n = 132)	p value
Age, mean ± SD, yr	12.6 ± 3.7	12.1 ± 4.1	0.49
Type 1 diabetes, n (%)			
New diagnosis	32 (55.2)	68 (51.5)	0.64
Established diagnosis	26 (44.8)	64 (48.5)	0.64
HgbA1c, mean ± SD, %*	12.9 ± 2.1	12.2 ± 1.9	0.04
SCr, mean ± SD, mg/dL	0.96 ± 0.4	0.89 ± 0.5	0.21
K+, mean ± SD, mEq/L	4.1 ± 0.8	4.3 ± 0.9	0.18
BUN, mean ± SD, mg/dL	15.0 ± 6.6	15.8 ± 8.6	0.49
pH, mean ± SD	7.1 ± 0.09	7.1 ± 0.11	0.78
CO_2, mean ± SD, mmol/L	7.8 ± 2.5	7.1 ± 2.6	0.12
Severity of DKA, n (%)			
Moderate	35 (60.3)	64 (48.5)	0.13
Severe	23 (39.7)	68 (51.5)	0.13
Initial IV insulin infusion dose, mean ± SD, unit/kg/hr	0.095 ± 0.01	0.092 ± 0.2	0.24
Home insulin glargine dose, mean ± SD, unit/kg	0.4 ± 0.2	0.4 ± 0.2	0.35
Time from admission to insulin glargine administration, mean ± SD, hr†	1.8 ± 3.4	24.4 ± 13.8	<0.001

BUN, blood urea nitrogen; CO_2, carbon dioxide; DKA, diabetic ketoacidosis; IV, intravenous; HgbA1c, hemoglobin A1c; K+, serum potassium; SCr, serum creatinine

* HgbA1c values were only available for 49 patients in the early insulin glargine group and 117 patients in the late insulin glargine group.
† In the early insulin glargine group, the range of time from admission to insulin glargine administration was prior to admission (0 hours) to 5.8 hours. In the late insulin glargine group, the range was 6.4 to 106.5 hours.

electrolyte additives at our institution were based on the patient's weight (< 35 kg or ≥ 35 kg) and initial serum potassium concentrations (Table 1). The IV insulin infusion was started at a rate of 0.1 unit/kg/hr in the majority of patients, although some patients received an initial dose of 0.05 unit/kg/hour. For patients with new-onset T1DM, insulin glargine was administered at 0.2 unit/kg. For patients with known T1DM, insulin glargine was administered per their home dosing.

A Student *t* test was used to assess the primary outcome. For secondary outcomes, χ^2 was used to calculate incidence of hypokalemia and hypoglycemia. Student *t* tests were used to assess time to resolution of ketoacidosis, length of PICU stay, length of hospital stay, total units of IV insulin infused, and average rate of blood glucose decline. Descriptive statistics were used to assess baseline characteristics. All statistical tests were 2-sided and were performed with a p value of < 0.05 indicating statistical significance. Results with normal distribution are presented as mean ± SD, and results without normal distribution are presented as median [IQR]. Statistical analysis was performed using Statistical Package for the Social Sciences version 19 (IBM, Armonk, NY).

Results

One hundred ninety patients were included in the study population and received insulin glargine while on IV insulin (see Supplemental Figure). Patients were excluded from the study if they received a continuous insulin infusion but they were not admitted for DKA (n = 445), were diagnosed with mild DKA (n = 81), were transferred to another hospital (n = 6), or had T2DM (n = 3). There were 58 patients who received early insulin glargine and 132 patients who received late insulin glargine.

Baseline characteristics were similar between the 2 groups (Table 2). The patients who received late insulin glargine had a higher proportion of patients with severe DKA, though the difference was not statistically significant. There was a statistically significant difference in the hemoglobin A1c because it was higher in those who received early insulin glargine compared with those who received late insulin glargine.

The median time on IV insulin was shorter in the patients who received early insulin glargine compared with those who received late insulin glargine (17.0 [IQR, 14–22.8] vs 22.9 hours [IQR, 4.3–29.3]; p = 0.0006) (Table 3). Resolution of DKA was also faster in patients

Table 3. Summary of Primary and Secondary Outcomes

Outcome	Early Insulin Glargine, n = 58	Late Insulin Glargine, n = 132	p value
Time on IV insulin infusion, median [IQR], hr	17.0 [14.–22.8]	22.9 [4.3–29.3]	0.0006
Time to resolution of DKA, median [IQR], hr	13.0 [9.8–16.8]	18.2 [12.5–27.6]	0.005
Length of hospital stay, median [IQR], days	3 [2–5]	3 [2–5]	0.56
Length of PICU, median [IQR], days	1 [0-2]	1 [0-2]	0.15
Total units of IV insulin infused, mean ± SD, unit/kg	1.74 ± 0.64	2.32 ± 1.34	0.002
Average rate of blood glucose decline, mean ± SD, mg/dL/hr	60.7 ± 21.9	49.9 ± 21.4	0.002
Incidence of hypoglycemia			
Incidence of BG < 60, n (%), mg/dL	3 (5.2)	11 (8.3)	0.655
Mean lowest BG while on IV insulin infusion, mean ± SD, mg/dL	104.0 ± 39.9	105.2 ± 35.8	0.834
IV dextrose administered, n, yes	0	1	1.000
Titrate IV insulin infusion rate, n (%)			
Increase	4 (6.9)	11 (8.3)	0.74
Decrease	22 (37.9)	53 (30.2)	0.77
No change	32 (55.2)	68 (51.5)	0.64
Incidence of hypokalemia			
Incidence of K < 3.5 mEq/L on IV insulin infusion, n (%)	37 (63.8)	86 (65.2)	0.857
Lowest K+ on IV insulin infusion, median [IQR], mEq/L	3.3 [2.9–3.7]	3.2 [2.9–3.7]	0.10
KCl administered, n (%), yes	4 (6.9)	17 (12.9)	0.226
KPhos administered, n (%), yes	4 (6.9)	21 (15.9)	0.091
Maximum K+ concentration in IV fluids, mean ± SD, mEq/L	32.1 ± 9.9	31.4 ± 0.1	0.688
Incidence of increasing K+ concentration in fluids, n (%)	3 (5.2)	16 (12.1)	0.141

BG, blood glucose; DKA, diabetic ketoacidosis; IV, intravenous; K+, serum potassium; KCl, potassium chloride; KPhos, potassium phosphate; PICU, pediatric intensive care unit

who received early insulin glargine compared with those who received late insulin glargine (median, 13.0 [IQR, 9.8–16.8] vs 18.2 hours [IQR, 12.5–27.6]; p = 0.005). The patients who received early insulin glargine received a lower total amount of IV insulin than those who received late insulin glargine (1.74 ± 0.64 vs 2.32 ± 1.34 unit/kg; p = 0.002). Median length of PICU stay (1 [IQR, 0–2] and 1 day [IQR, 0–2]; p = 0.15) and median length of hospital stay (3 [IQR, 2–5] and 3 days [IQR, 2–5]; p = 0.56) were similar between the 2 groups.

Among those who received early insulin glargine, there were 3 episodes of hypoglycemia, compared with 11 episodes of hypoglycemia in those who received late insulin glargine (p = 0.655). The mean lowest BG while on IV insulin was similar between the 2 groups (104 ± 39.9 vs 105 ± 35.8 mg/dL; p = 0.834). One patient in the late insulin glargine group required an IV dextrose bolus for management of hypoglycemia, whereas no patients in the early insulin glargine group required an IV dextrose bolus for treatment for hypoglycemia.

The incidence of hypokalemia while on IV insulin was similar between the 2 groups (63.8% vs 65.2%; p = 0.857) and the lowest median serum potassium concentration while on IV insulin was also similar between the 2 groups (3.3 [IQR, 2.8–3.8] vs 3.3 mEq/L [IQR, 2.6–3.9]; p = 0.10). In the early insulin glargine group, 4 received potassium supplementation external to potassium being administered through IV fluids, compared with 17 in the late insulin glargine group (6.9% vs 12.9%; p = 0.226). Rates of potassium phosphate supplementation were higher in the late insulin glargine group (4 vs 21 doses [6.9% vs 15.9%]; p = 0.091). Of the patients who received early insulin glargine, 3 required an increase in the potassium concentration of the IV fluids via the 2-bag method, compared with 16 up-titrations in potassium concentration in the patients who received late insulin glargine (5.2% vs 12.1%; p = 0.141).

Discussion

Pediatric patients with moderate to severe DKA who received early insulin glargine had a significantly shorter time on IV insulin infusion, as well as significantly faster time to resolution of DKA, when compared with those who received late insulin glargine. Although not statistically significant, patients who received early insulin glargine showed a numerical trend toward lower incidence of hypoglycemia and hypokalemia than those who received late insulin glargine, suggesting that early insulin glargine administration is safe. Our findings are

consistent with current pediatric and adult data available for the concurrent administration of insulin glargine with IV insulin in the treatment of DKA.

At the time of this study publication, there are 2 studies in adult patients evaluating insulin glargine plus IV insulin infusion administration. A prospective, randomized controlled trial of 40 adult patients with DKA evaluated time to closure of anion gap. All patients received IV insulin infusion and the experimental group received insulin glargine within 2 hours of diagnosis. The estimated time to closure of anion gap and hospital stay were shorter in the insulin glargine group, with similar rates of hypoglycemia and ICU length of stay. They concluded that further data were needed to determine efficacy.[6] A 2012 prospective randomized study of 61 patients with diabetes aimed to determine the rates of rebound hyperglycemia (defined as BG > 180 mg/dL in the 12 hours after discontinuation of insulin infusion) with early insulin glargine. They evaluated patients receiving IV insulin infusion vs IV insulin infusion plus insulin glargine 0.25 unit/kg within 12 hours of initiation of IV insulin infusion.[7] Twenty-five patients were receiving insulin for DKA, with 13 in the IV insulin only group and 12 in the IV insulin infusion plus insulin glargine group. They found that patients who received IV insulin infusion plus insulin glargine had significantly lower rates of rebound hyperglycemia, as well as nonsignificant shorter time on IV insulin infusion and no episodes of hypoglycemia in the IV insulin infusion plus insulin glargine group. Although incidence of rebound hyperglycemia was not collected in this retrospective review, it could potentially be an additional benefit in early insulin glargine administration. Both adult studies concluded that early insulin glargine administration was safe in terms of avoiding glycemic abnormalities, which is consistent with our study findings.

There are 2 studies of pediatric patients evaluating the administration of early insulin glargine in the management of DKA. In a 2007 retrospective cohort study, Shankar et al[3] observed that in children who received 0.3 unit/kg of subcutaneous insulin glargine within the first 6 hours of diagnosis of DKA, in addition to IV insulin, demonstrated a shorter mean time to acidosis correction, a lower total amount of insulin infused, a shorter insulin infusion time, and a trend toward a shorter hospital stay when compared with patients who did not receive insulin glargine within the first 6 hours. It should be noted as a limitation that only 12 patients received early insulin glargine compared with 59 patients who received insulin glargine more than 6 hours after admission. Our study demonstrated similar trends with early insulin glargine administration, including shorter time to resolution of DKA and shorter time on IV insulin. Further, in a 2017 retrospective chart review, Harrison et al[4] compared children presenting to the emergency department in DKA who received insulin glargine ≥ 4 hours before discontinuation of IV insulin (n = 55) with those who received insulin glargine ≤ 2 hours or no subcutaneous insulin before the cessation of the IV insulin (n = 94). Their study objective was to determine if early insulin glargine was associated with an increased risk of hypoglycemia, hypokalemia, or other complications. In their study, duration of DKA and time on IV insulin was longer in the insulin glargine ≥ 4 hours group, and trends in acidosis resolution and incidence of hypoglycemia were similar between the 2 groups, suggesting that early glargine administration is safe and prompting the need for additional data on efficacy of early insulin glargine in DKA.

Previous data have demonstrated that hypokalemia may be a concern with early insulin glargine administration. Harrison et al[4] demonstrated that hypokalemia (serum potassium concentration < 3.5 mEq/L) occurred more often in patients in their early insulin glargine administration group; however, no cardiac arrhythmias were reported in any patient. Several measures to assess hypokalemia were collected in our retrospective cohort study. Our results showed similar proportions of patients in both groups that experienced a potassium < 3.5 mEq/L while on IV insulin. Patients who received late insulin glargine required more increments of both potassium chloride and potassium phosphate, as well as a higher rate of increasing potassium concentrations via the 2-bag method. Unlike the results reported by Harrison et al,[4] the results of our study did not demonstrate an increased incidence of hypokalemia in patients who received insulin glargine early in the management of DKA. This difference in incidence of hypokalemia could be due to a variety of factors. In the Harrison et al[4] study, all patients received an initial rate of IV insulin at 0.1 unit/kg/hr; in our study, 27 patients (14%; 6 in the early glargine group [10%] vs 19 in the late glargine group [14%]) received IV insulin at 0.05 unit/kg/hr as the initial dose. Because higher IV insulin infusion rates have been associated with higher rates of hypokalemia,[9,10] this may be a possible factor in describing differences in rates of hypokalemia between studies. Another factor to consider is the study duration: the Harrison et al[4] study collected serum potassium measurements from the start of the IV insulin infusion until 24 hours post-discontinuation; our study only collected serum potassium measurements while patients were receiving IV insulin, so there could have been episodes of hypokalemia in our patients after discontinuing the IV insulin infusion that are not reported in this study.

In our study, patients who received early insulin glargine had a lower total dose of insulin by weight that may be attributed to a shorter time on IV insulin infusion. These patients had similar PICU and hospital lengths of stay. These results should be interpreted with the consideration that patients with new-onset T1DM may have longer stays due to the need for diabetes education, as well as the larger proportion of patients in the late insulin glargine group with severe DKA compared with the early insulin glargine group. Although this study was not designed to assess cost-savings, based

on a numerical trend toward a slightly shorter length of PICU and hospital stays, there may be cost-savings associated with early administration of insulin glargine in the management of DKA. Future research may consider evaluating cost-savings implications of these outcomes.

Several limitations exist for this retrospective cohort study. The rate changes of the dextrose-containing bag as part of a 2-bag method were not collected due to the frequency of rate changes that often occur. Patients who may have presented to an outside hospital with moderate or severe DKA may have been transferred to this academic medical center, where their DKA may have partially resolved and demonstrated a lower severity, resulting in exclusion from the study or categorization into a less severe DKA group. Some patients received insulin glargine prior to admission, typically at an outside hospital or en route to the hospital, so the time from admission to insulin glargine administration was unknown and therefore recorded as zero because that was deemed the most conservative method to avoid bias. The IV insulin infusion rate was titrated down more frequently in patients who received early insulin glargine, so this could have resulted in lower rates of hypoglycemia (Table 3). Although adjusting the IV insulin infusion rate may not be widely practiced, this was a practice followed at our institution and should be considered when interpreting results of this study. Because hypoglycemia has been noted as a concern for insulin glargine administration as part of management of DKA, IV dextrose administration was collected and reported, but oral dextrose was not collected for hypoglycemia management. This data point was not collected due to inconsistent documentation of administration of oral dextrose on the electronic health record. Additionally, since we did not have the ability to collect administration of all oral dextrose formulations, including juice, food, and oral dextrose gel, this was another reason for excluding them entirely. Rates of cerebral edema were not collected due to lack of feasibility because the suspicion and/or confirmation of cerebral edema may be documented in various places in the electronic health record. Finally, because a diabetic educator is not available for education on the weekends, those admitted with a new diagnosis of T1DM may have experienced a longer hospital stay in order to receive new onset diabetes education prior to discharge. In the late insulin glargine group, 28% (n = 37) of patients had their IV insulin infusion discontinued on a Friday, Saturday, or Sunday and were discharged on a following weekday. There was a similar rate in the early glargine group (31%, n = 18). There was a slightly higher rate of newly diagnosed T1DM in the early insulin glargine group, although not statistically significant.

Conclusion

This study built upon the limited existing data that the administration of early insulin glargine for management of DKA is safe and could facilitate faster resolution of moderate to severe DKA in pediatric patients. Although not demonstrated in this study, clinicians should closely monitor for signs of hypokalemia in patients receiving early insulin glargine while on IV insulin for management of DKA; a higher incidence of hypokalemia has been previously reported to be associated with such administration for DKA. Further research should focus on cost savings associated with early insulin glargine administration as part of DKA management.

Article Information

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Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. Kelli Jo Welter, Ellen Bickel, Jessica Marquez, and Patricia Marshik had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. The study was approved by the Institutional Review Board with the need for informed consent waived.

Acknowledgments. The authors would like to thank Jason Koury, PharmD, RN, BCPPS, and Preeyaporn Sarangarm, PharmD, BCPS, BCCCP for their support and guidance.
A virtual poster presentation of objectives and methods was presented at the American Society of Health System Pharmacists Midyear Clinical Meeting on December 6, 2020.

Submitted. January 24, 2022

Accepted. April 7, 2022

Supplemental Material. DOI: 10.5863/1551-6776-28.2.149.S

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