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# **Diabetes Technology in the Inpatient Setting for Management of Hyperglycemia**

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#### **Keywords**

Diabetes; Technology; Inpatient; Hospital; Glycemic control

### **INTRODUCTION**

Advances in diabetes technology over the past decades have revolutionized patient care and diabetes management. The use of this technology, including continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII), in patients with type 1 (T1) and type 2 (T2) diabetes mellitus (DM) continues to grow in the ambulatory setting. Although substantial data support outpatient use of this technology for improvement in glycemic control and diabetes outcomes, there are limited data regarding its use in the inpatient setting.<sup>1</sup> There is consensus among experts and medical societies that, compared with intermittent capillary blood glucose testing, CGM technology offers benefits in the prevention of severe hyperglycemia and hypoglycemia by identifying glucose trends and allowing insulin doses to be adjusted more accurately.<sup>2–4</sup> In addition, several diabetes clinical guidelines support the continued use of outpatient CSII in patients who are physically able to continue using their insulin pump during hospitalization.<sup>3,5</sup> However, randomized controlled trials are needed to determine whether use of CGM and CSII systems in the hospital can improve clinical outcomes compared with intermittent capillary blood glucose monitoring and conventional insulin treatment. As CGM and CSII technologies continue to advance, the use of artificial pancreas technology is being evaluated in the inpatient setting. Use of computerized decision support systems for glycemic control in the hospital is also expanding. Here we review current available diabetes technology as it relates to the management of hospitalized patients.

### **CONTINUOUS GLUCOSE MONITORING IN THE HOSPITAL**

The use of capillary point-of-care (POC) glucose testing has been the mainstay for monitoring and treatment of hospitalized patients with diabetes. POC blood glucose (BG) testing is commonly performed 3 to 4 times daily in hospitalized patients for monitoring of

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glycemic control and adjustment of diabetes treatment regimens. However, the need for frequent BG testing in certain inpatient populations, the intermittent nature of testing, and the associated time burden for nursing and ancillary hospital staff are significant limitations of POC BG testing. The desire for closer monitoring of glucose values led to the development of CGM beginning in the late 1970s, with approval of the first CGM by the Food and Drug Administration occurring in 1999.<sup>6</sup> The ability of CGM to provide estimated glucose values every 5 to 15 minutes with information regarding glucose trends allows for a more comprehensive assessment of glycemic control, an attractive feature in both inpatient and outpatient settings. Rapid improvements in accuracy and increased commercial availability of CGM technology has led to its widespread use in ambulatory diabetes management. However, use of CGM in the hospital remains investigational, with ongoing studies evaluating its use in diverse inpatient populations.

In the hospital setting, several studies have shown improvement in the detection of both hyperglycemia and hypoglycemia in critically ill and non-critically ill patients.<sup>2,7–9</sup> In contrast to the exclusive use of subcutaneous CGM sensors in the outpatient realm, CGM use in the hospital can also include invasive (intravascular) or noninvasive (transdermal) CGM in intensive care unit (ICU) settings.

Most studies in ICU populations using CGM have focused on accuracy and reliability, and have in general been small and underpowered to detect changes in patient-centered outcomes (ie, incidence of hypoglycemia or complications) (Table 1). Of the studies assessing glycemic control, most did not show significant differences in average glycemic control with CGM versus POC glucose testing. Kopecky and colleagues<sup>12</sup> investigated the use of CGM combined with an enhanced model predictive control (eMPC) insulin titration algorithm in postoperative cardiac ICU patients. The use of the eMPC algorithm combined with CGM was compared with standard use of the algorithm with interval POC glucose testing (control group). Overall, there were no significant differences in glycemic control between the eMPC-CGM system with more frequent input of glucose values compared with the eMPC algorithm with intermittent BG values alone.<sup>12</sup> In a larger study, Holzinger and  $colleagues<sup>11</sup>$  observed a significant reduction in hypoglycemia (defined as glucose <40 mg/dL or 2.2 mmol/L) with real-time CGM (RT-CGM) use versus POC testing (1.6 vs 11.5%;  $P = .031$ ) in ICU patients requiring mechanical ventilation. A subgroup analysis in this population revealed improved glycemic control and time in target glucose range (defined as glucose  $\langle 110 \text{ mg/d}$ L or 6.1 mmol/L) in patients with higher illness severity indices. Despite these findings, there were no differences in hospital length of stay (LOS) or mortality between CGM and POC BG testing groups.<sup>11</sup> A recent expert consensus meeting acknowledged that use of CGM in critical care populations appears to be accurate and reliable, but there continues to be a need for larger studies powered to determine efficacy in improving glycemic control, detection and reduction of hypoglycemic events, and impact on hospital stay and clinical outcomes.<sup>2</sup>

In non-critically ill hospitalized patients, studies with the use of CGM have been mostly observational (Table 2). Observational data have provided important insight into glycemic control patterns in hospitalized patients, emphasizing improved detection of hypoglycemia using CGM. Gomez and Umpierrez<sup>7</sup> compared the use of blinded/professional CGM versus

POC glucose testing in non-critically ill hospitalized patients with T2DM treated with basal bolus insulin regimens. Even though there was no significant difference in mean daily blood glucose concentration between groups, CGM detected a higher number of hypoglycemic events (52 vs 12,  $P = .0001$ ). More than 50% of the hypoglycemic events occurred between dinner and breakfast, highlighting the utility of CGM use for detection of nocturnal hypoglycemia in this population.<sup>7</sup> A recent pilot study by Spanakis and colleagues<sup>19</sup> in a population of non-ICU hospitalized older adult patients (mean age  $70.8 \pm 6.2$  years) demonstrated feasibility of using CGM data transmitted to nursing personnel in a telemetrytype method, with an alert for hypoglycemia set at a sensor glucose value of 85 mg/dL (4.7 mmol/L). In this group of 5 patients on insulin therapy, there were no episodes of severe hypoglycemia (<54 mg/dL or 3 mmol/L) and potential hypoglycemic episodes were prevented in 2 patients using the CGM alert system during the hospital stay.<sup>19</sup>

CGM technology continues to evolve, with investigations expanding to more diverse inpatient populations with diabetes. More accuracy data are needed in specific hospital patient populations, including those with severe dehydration and volume depletion, anasarca, and end-stage renal disease on hemodialysis or peritoneal dialysis. Although CGM metrics (including time in target glucose range, time in hyperglycemia, time in hypoglycemia, and glycemic variability) continue to be updated and defined for targeting improved glycemic control and outcomes in ambulatory patients,20 no current consensus exists regarding CGM metrics in hospitalized patients. Further information is needed in this setting on standardization of glycemic control metrics, appropriate target glucose ranges, and impact of CGM use on hospital outcomes and costs to understand how to safely and effectively implement this technology. In addition to targeting improved glycemic control, emerging CGMs that no longer require calibration with POC glucose testing (factory-calibrated) have the potential to decrease both nursing and patient burden associated with frequent POC glucose testing in the hospital. Ongoing studies ([NCT03832907](https://clinicaltrials.gov/ct2/show/NCT03832907)) with factory-calibrated CGM are testing its accuracy in diverse inpatient populations, and the use of CGM data by nursing and ancillary staff to detect and prevent glycemic excursions [\(NCT03877068](https://clinicaltrials.gov/ct2/show/NCT03877068)).

### **CONTINUOUS SUBCUTANEOUS INSULIN INFUSION IN THE HOSPITAL**

With the use of CSII increasing in the ambulatory setting, the importance of guidelines for its continued use in the inpatient setting for health care providers has been addressed by several professional societies, including the American Diabetes Association, the American Association of Clinical Endocrinologists, and The Endocrine Society. These societies advocate for continuation of CSII therapy in appropriate hospitalized patients, with the support of (1) implemented hospital policies on CSII, (2) inpatient endocrinology or diabetes management teams, and (3) a signed agreement from the patient acknowledging responsibilities of CSII therapy.<sup>3,5,21</sup> Continuation of CSII is not recommended in critically ill and hemodynamically unstable patients, as well as in those who are not able to demonstrate appropriate use of their insulin pump.<sup>1,3,5</sup> For instance, a retrospective analysis of 50 patients by Kannan and colleagues<sup>22</sup> demonstrated that 24% of patients admitted to the hospital using CSII in the outpatient setting were unable to correctly demonstrate use of critical pump skills during hospitalization. A recent review by Umpierrez and Klonoff<sup>1</sup>

illustrates a proposed algorithm for decision-making regarding hospital continuation of CSII therapy (Fig. 1), as well as contraindications to its use (Box 1).

Most of the data regarding hospital use of CSII have been retrospective and focused on the continuation of outpatient CSII during admission. These studies have suggested that with appropriate patient selection and hospital guidelines, patients on preexisting CSII (with or without concurrent CGM) can safely maintain glycemic control during hospitalization. Review of 125 hospitalizations of 65 patients on insulin pump therapy by Nassar and colleagues<sup>23</sup> showed an increase in prevalence of insulin pump use during hospitalization over a 3-year period. During this time, there were no significant differences in mean hospital glucose levels between patients who continued CSII versus those transitioned to multiple daily insulin injections (MDI).<sup>23</sup> An additional review by Cook and colleagues<sup>24</sup> of 253 hospitalizations of 136 patients on outpatient CSII over a 6-year period showed similar results regarding glycemic control between CSII use and subcutaneous insulin therapy during hospitalization, but there were fewer severe hyperglycemic (BG >300 mg/dL or 16.7 mmol/L) and hypoglycemic (BG <50 mg/dL or 2.8 mmol/L) events in patients remaining on CSII in the hospital. In addition, a recent prospective pilot trial by Levitt and colleagues<sup>25</sup> investigated the feasibility of CSII, both with and without CGM technology, in hospitalized patients with T2DM. Patients were randomized to 3 groups: (1) basal bolus insulin therapy with blinded CGM, (2) CSII with blinded CGM, or (3) CSII with RT-CGM. Although there were no significant differences in time in target glucose range or time in hypoglycemia between groups, this study showed the feasibility of combined CSII-CGM therapy in the inpatient setting. In addition, they reported that CGM detected more episodes of hypoglycemia than POC glucose testing alone (19 vs 12 episodes).25 A study by Gu and colleagues<sup>18</sup> in China evaluated CSII with CGM versus MDI in non-acutely ill patients with T2DM hospitalized for glycemic optimization over a 2-week period. In 81 patients (40 on CSII-CGM vs 41 on MDI), more patients using CSII-CGM were able to achieve target glucose values between 70 and 180 mg/dL (3.9–10.0 mmol/L) within a 3-day period compared with those on MDI (53% vs 15%, respectively). Overall, those on CSII-CGM also had significantly less hypoglycemia (glucose <50 mg/dL [2.8 mmol/L]; 0.02 vs 0.31%,  $P\leq$ .05), and less severe hyperglycemia (glucose >250 mg/dL [13.9 mmol/L]; 3.9 vs 8.3%,  $P \le 0.05$ ).<sup>18</sup>

Although CSII does continue to be used in the inpatient setting, current investigations are moving toward the use of combined CSII-CGM technology with the ability to provide automated modulation of subcutaneous insulin infusion rates (ie, closed-loop or hybrid closed-loop technology).

#### **ARTIFICIAL PANCREAS TECHNOLOGY IN THE HOSPITAL**

The artificial pancreas system, also referred to as a "closed-loop" system, "automated insulin delivery" system, or "autonomous system for glycemic control," is composed of a CGM and insulin infusion pump for CSII. Insulin delivery is regulated by a computer algorithm that determines the amount of insulin to administer in response to a given sensor glucose concentration, thereby more closely approximating physiologic insulin action. Initial studies evaluating the use of a closed-loop system in the hospital setting focused on critically ill

patients. These small, randomized trials demonstrated good efficacy data with improvement in time in target glucose range, and lower mean glucose levels without an increased risk of hypoglycemia.26–28

More recent studies by Hovorka and colleagues $29-32$  evaluating the use of a closed-loop system in the non-critically ill hospital setting have shown promising safety and efficacy data. In one study, patients with T2DM were randomized to receive conventional insulin treatment or insulin delivery based on a closed-loop system with ad lib meal intake and activity. Findings from the initial pilot study of 40 patients demonstrated a greater percentage of time spent with sensor glucose in target range (100–180 mg/dL or 5.6–10.0 mmol/L) in the closed-loop intervention compared with control, 59.8% versus 38.1%, and less time in hyperglycemia (difference of  $19\%$ ).<sup>31</sup> There was no significant difference in mean BG between groups or hypoglycemia rates, and no significant differences in insulin doses. Glucose variability was decreased in the closed-loop group. Patients were overwhelmingly satisfied with the use of the closed-loop system.<sup>31</sup> Similar findings were seen in a larger multicenter study implementing the same protocol with improvement in time in target glucose range in the closed-loop group compared with controls  $(65.8\% \pm 16.8\% \text{ vs } 10.8\%)$ 41.5%  $\pm$  16.9%, 95% confidence interval [CI], 18.6 to 30.0; *P*<.0013).<sup>29</sup> A post hoc analysis in patients with T2DM admitted to the hospital on hemodialysis found that patients randomized to the closed-loop system spent 37.6% more time with sensor glucose in target range compared with standard-of-care POC glucose monitoring without an increased risk of hypoglycemia.<sup>32</sup>

Nutritional support, either through parenteral or enteral routes, frequently results in hyperglycemia in patients with and without a prior diagnosis of diabetes.<sup>33</sup> Unique challenges exist in this population in that unplanned interruptions in feedings can place patients at risk for hypoglycemia. Use of a closed-loop system in the setting of nutritional support resulted in improved glycemic control with a higher proportion of time with glucose in target range (68.4% [standard deviation (SD) 15.5] vs 36.4% [SD 26.6], P<.0001), lower mean glucose (153 mg/dL [SD 1.2] vs 205 mg/dL [SD 3.4], 8.5 vs 11.4 mmol/L,  $P = .001$ ), lower rates of hyperglycemia (32.6% less time with glucose >180 mg/dL or 10.0 mmol/L [95% CI 17.8–47.3], P<.0001), although no difference in hypoglycemia when compared with conventional insulin treatment.<sup>30</sup>

A recent observational study reported glycemic control of patients with T1DM ( $N = 27$ ) who participated in randomized crossover trials during pregnancy using closed-loop during labor, delivery, and postpartum.<sup>34</sup> Use of closed-loop was associated with  $82.0\%$  (interquartile range [IQR] 49.3, 93.0) time in target glucose range during labor and delivery and a mean glucose of  $124 \pm 25$  mg/dL (6.9  $\pm$  1.4 mmol/L). Closed-loop resulted in good glycemic control throughout vaginal, elective, and emergency cesarean deliveries. After delivery, women spent 83.3% of time in target glucose range (70–180 mg/dL or 3.9–10.0 mmol/L).<sup>34</sup>

Potential advantages to using a closed-loop system in the hospital setting include the ability to continually adapt insulin administration to changing glucose levels with minimal input from nursing or support staff. Use of a closed-loop system means less active management for nursing staff and therefore less risk of dosing errors compared with MDI or intravenous

insulin administration, with improved glycemic control outcomes and a lower risk of iatrogenic hypoglycemia. Previous randomized controlled trials have been limited to patients with T2DM, and have mostly excluded patients with T1DM, which may be a more vulnerable population. There is concern with regard to pump or sensor failure and the need for device removal given the associated potential for diabetic ketoacidosis. Among closedloop studies, up to 27% of patients had devices removed at least once during hospitalization.  $29$  It is also important to note that limited data exist evaluating the impact of a closed-loop system on clinical outcomes and hospital costs. These data will be essential to justify widespread adoption of such technology, given high implementation costs and need for specialized training for health care staff.

# **COMPUTERIZED DECISION SUPPORT SYSTEMS FOR GLYCEMIC CONTROL IN THE HOSPITAL**

The need for frequent hospital glucose monitoring and insulin titration to maintain glycemic control while avoiding hypoglycemia with the use of intravenous insulin infusion has triggered the emergence of computerized insulin dosing systems, also known as computerized decision support systems for glycemic control.<sup>35</sup>

Several systems have become commercially available to assist with glycemic management in critically ill patients with hyperglycemia, such as Glucommander (Glytec, Greenville, SC), EndoTool System (MD Scientific LLC, Charlotte, NC), and GlucoStabilizer (Medical Decision Network, Charlottesville, VA). In addition, several institutions have developed their own computerized insulin protocols and have integrated these systems into their electronic medical record (EMR), including, among others Vanderbilt University Hospital,<sup>36</sup> Medical University of South Carolina, <sup>37</sup> Tuft Medical Center, <sup>38</sup> and Kaiser Sunnyside Medical Center<sup>39</sup> (Table 3).

These systems aim to direct the nursing staff on adjusting insulin infusion rates and frequency of glucose testing to optimize inpatient glycemic control and alleviate some of the increased burden of nursing care associated with titrating insulin infusions in medical or surgical critical care units. The software considers previous glucose values and recommends changes in insulin infusion based on a dynamic insulin sensitivity multiplier derived from glucose changes after insulin dose adjustments.48 Most of the software is based on proportional-integral-derivative algorithms.

Several prospective and observational studies in critically ill patients,  $40-43,49$  burn unit patients, $47$  and patients with diabetic ketoacidosis<sup>44</sup> have reported that use of these systems resulted in improved glycemic control with low rates of hypoglycemia, and also less glycemic variability, when compared with standard paper-based algorithms.

Some systems also include algorithms for the management of hyperglycemia in noncritically ill patients treated with basal bolus insulin regimens, such as the Gluco-Tab (Joanneum Research GmbH [Graz, Austria] and Medical University of Graz) and Glucommander.<sup>50–52</sup> As shown in the critically ill population, these computerized decision

support systems can improve protocol adherence and glycemic control without increased rates of hypoglycemia.<sup>52</sup>

Still, most institutions use standard paper-based, nursing-driven protocols, likely due to the added licensing and implementation costs associated with these systems. There are also considerations regarding compatibility requirements for integration with the electronic medical records system at each individual institution. These devices may be useful in hospitals without diabetes management teams or diabetes experts on staff; however, considerations need to be given to the potential added costs and implementation needs.

### **SUMMARY**

The rapid evolution of diabetes technology during the past decades has led to increased use of CGM and CSII in the ambulatory setting for management of both T1DM and T2DM. In this volume of the *Endocrine Clinics*, experts have extensively reviewed benefits of outpatient diabetes technology use and the development of new CGM-derived glycemic control metrics. Expanding use of CGM and CSII technology has emphasized the need for more evidence regarding the continuation of these therapies during hospitalization. Recent data in hospitalized patients have shown remarkable progress in the use of diabetes technology in the hospital, including (1) improved accuracy and reliability of CGM, (2) safety of CSII in appropriate hospital populations, (3) improvement of glycemic control with computerized glycemic management systems in ICU and non-ICU settings, and (4) feasibility of inpatient CGM-CSII closed-loop systems for inpatient glycemic control. Ongoing studies are focusing on continued translation of this technology to improve glycemic control and outcomes in hospitalized patients.

# **DISCLOSURE**

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#### **Box 1**

#### **Contraindications to insulin pump therapy in the hospital**

Impaired level of consciousness (except during short-term anesthesia)

Patient's inability to correctly demonstrate appropriate pump settings

Critical illness requiring intensive care

Psychiatric illness that interferes with a patient's ability to self-manage diabetes

Diabetic ketoacidosis and hyperosmolar hyperglycemic state

Refusal or unwillingness to participate in self-care

Lack of pump supplies

Lack of trained health care providers, diabetes educators, or diabetes specialist

Patient at risk for suicide

Health care decision

From Umpierrez GE, Klonoff DC. Diabetes Technology Update: Use of Insulin Pumps and Continuous Glucose Monitoring in the Hospital. Diabetes Care. 2018;41(8):1579– 1589; with permission.

#### **KEY POINTS**

- **•** Ambulatory use of diabetes technology, including continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), and closed-loop systems, has rapidly expanded during the past decades, with more recent studies evaluating its translation to the hospital setting.
- **•** Preliminary data show improvement in detection of both hyperglycemia and hypoglycemia with use of CGM in the hospital.
- **•** Recent studies have tested the use of closed-loop systems in diverse populations of hospitalized patients.
- **•** Further investigation is needed regarding the inpatient use of diabetes technology and how it pertains to glycemic control and patient-centered outcomes.



#### **Fig. 1.**

Algorithm for inpatient continuation of CSII-CGM therapy hospitalization. EGD, upper endoscopy; IV, intravenous. (From Umpierrez GE, Klonoff DC. Diabetes Technology Update: Use of Insulin Pumps and Continuous Glucose Monitoring in the Hospital. Diabetes Care. 2018;41(8):1579–1589; with permission.)



**Table 1**

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ICU CGM outcomes studies ICU CGM outcomes studies



Abbreviations: CGM, continuous glucose monitoring; DM, diabetes mellitus; eMPC, enhanced model predictive control; ICU, intensive care unit; LOS, length of stay; RCT, randomized-controlled trial; RT-Abbreviations: CGM, continuous glucose monitoring; DM, diabetes mellitus; eMPC, enhanced model predictive control; ICU, intensive care unit; LOS, length of stay; RCT, randomized-controlled trial; RT-CGM, real-time continuous glucose monitoring. CGM, real-time continuous glucose monitoring.

Data from Refs. 10-14 Data from Refs.10–14

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**Table 2**

Non-ICU CGM studies Non-ICU CGM studies



Abbreviations: BG, blood glucose; CGM, continuous glucose monitoring; CGMS, continuous glucose monitoring system; ICU, intensive care unit; MDI, multiple daily injections; POC, point of care; SAP, sensor-augmented pump; T1 Abbreviations: BG, blood glucose; CGM, continuous glucose monitoring; CGMS, continuous glucose monitoring system; ICU, intensive care unit; MDI, multiple daily injections; POC, point of care; SAP, sensor-augmented pump; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus;

Data from Refs. 15-19 Data from Refs.15–19



**Table 3**

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 $^4\mbox{BG}$  presented in mg/dL (conversion: mg/dL<br>  $\times$  0.0555 = mmol/L). BG presented in mg/dL (conversion: mg/dL  $\times$  0.0555 = mmol/L).

Data from Refs. 37,38,40-47 Data from Refs.37,38,40–47  $b_{\rm Range}$  not described. Range not described.  $c_{(P<.05)}$