COMMENTARY

The Impact of COVID-19 on CGM Use in the Hospital

Nicole Ehrhardt and Irl B. Hirsch

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In 1995 the movie *Outbreak* was released, and we shivered but were amused. The fictional virus "Motaba" was soon replaced by the very real H1N1, severe acute respiratory syndrome coronavirus (SARS-CoV, which causes SARS), and Ebola. Fortunately, the overall devastation of these potential pandemics, with the concern of deaths in the thousands or millions, never materialized. However, now the world is faced with SARS-CoV-2, the virus known to cause coronavirus disease 2019 (COVID-19), and the 2020 "Outbreak" movie is not fictional. This virus is real, and we are racing to find ways to save lives from this deadly disease while protecting the health and well-being of frontline health care workers.

There is now a strong body of evidence that diabetes, established cardiovascular disease, and other metabolic risk factors (particularly visceral fat accumulation) are associated with increased risk of need for mechanical ventilation, acute kidney injury, and mortality (1–4). Hyperglycemia during hospitalization for COVID-19 has also been established as a poor prognostic indicator (4,5). Some studies report that those with previously poorly controlled diabetes tend to have higher morbidity and mortality (4). However, another recent study found that previous insulin use, not HbA_{1c}, was a predictor of mortality (6). More recently reported was that COVID-19 survivors had lower mean glucose during hospitalization than nonsurvivors (7). This finding brings some of the old controversy about glycemic management in the hospital to light, raising the question of whether lowering glycemic goals may help mitigate the acute on top of chronic inflammatory response and improve outcomes.

A report in 2001 on critically ill surgical patients gained wide attention (8). Intensive insulin therapy in the intensive care unit (ICU) improved morbidity and mortality, and much of the diabetes world extrapolated these findings to all patients in all hospitals. Unfortunately, this single-center study could not be replicated in other patient populations and in multicenter trials (Fig. 1). Later studies showed only improvement in mean glucose, but at the cost of increased hypoglycemia (9–12). The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial actually reported an increase in mortality associated with a high incidence of hypoglycemia (12). The reasons for the hypoglycemia in these ICU patients are likely multifactorial. Using standardized protocols for a multicenter study where each site has its own separate algorithm makes nursing acceptance difficult. The necessary frequency of glucose measurements in patients using intravenous insulin was not as well understood as it is today. Perhaps most importantly, fingerstick glucose measurements in the ICU every hour could often be delayed for many hours, placing the patient at a higher risk for hypoglycemia. It was opined that we would not be able to answer questions about the impact of near-normal glycemia in the hospital until continuous glucose monitoring (CGM) was available (13).

Two decades ago, CGM was introduced (initially masked to the patient), and since then glucose monitoring technology has advanced rapidly. Currently, CGM has 10- to 14-day sensor wear, no need for calibration, and increased accuracy allowing nonadjunctive use (14). For the last decade there have been ongoing discussions about inpatient use of CGM (real-time) in both the ICU and non-ICU settings. CGM should theoretically minimize both hyperglycemia and hypoglycemia. Unfortunately, conflicting reports on hypoglycemia benefits and poor accuracy of the older technology generated little enthusiasm for wide uptake of CGM in the hospital (15).

The COVID-19 pandemic has brought a new urgency to the need to assess the feasibility of CGM in the hospital to preserve personal protective equipment (PPE) and limit health care workers' exposure. Achieving even standard glycemic control of 7.8–10.0 mmol/L (140–180 mg/dL) is now a challenge for many

University of Washington Medicine Diabetes Institute, Seattle, WA

Corresponding author: Irl B. Hirsch, ihirsch@uw.edu

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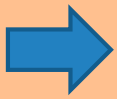
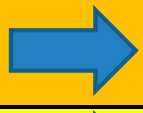
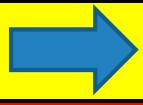
Reference/ year/ number of sites	Total participants in intervention arm (*n*) % diabetes	Delta change in mean glucose, intervention vs. control (mg/dL)	Ratio severe hypoglycemia, intervention vs. control	Mortality
(8) Van den Berghe et al. 2001 1 site	765 13% DM	50	6.6	
(9) Van den Berghe et al. 2006 1 site	595 17% DM	52	5.8	
(10) VISEP 2008 18 sites	247 31% DM	39	4.1+	
(11) Glucontrol 2009 21 sites	536 16% DM	29	3.2	
(12) NICE-SUGAR 2009 42 sites	3016 20% DM	29	13.6	

+ early termination of study due to hypoglycemia

Figure 1—Glycemic metrics in critical care randomized trials. DM, diabetes mellius; VISEP, Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis.

hospitals in both the ICU and non-ICU areas for those infected with COVID-19. In the report by Bode et al. (16), in 184 patients with diabetes or uncontrolled hyperglycemia, 39% of the glucose levels were >10 mmol/L (180 mg/dL), 13.5% were >13.9 mmol/L (250 mg/dL), and 1% were <3.9 mmol/L (70 mg/dL) (16).

Certainly, maintaining good glycemic control is difficult in the era of COVID-19, made even more challenging given the collective trauma suffered by the medical community from NICE-SUGAR. Our current "primum non nocere" has become "give insulin but at all costs avoid hypoglycemia." There has been a bolus of recent reports on CGM in the hospital. The need to minimize PPE use and reduce exposure has accelerated reporting on these studies as the goal is to manage glucose remotely, even more safely and effectively, without definitive data that near-normal glycemia will improve outcomes.

Overall, the recent reports published in *Diabetes Care* are encouraging. Nair et al. showed that in hospitalized patients after surgery, the Dexcom G6 had a mean absolute relative difference (MARD) of 9.4% (17), and Reutrakul et al. also demonstrated a MARD of 9.77% in COVID-19 patients (18); both results are similar to the value indicated on the sensor's label (19). These studies are promising as they show that CGM accuracy may have improved enough to be used in the hospital setting. However, we acknowledge that hypoglycemia in these studies was limited and thus accuracy with hypoglycemia was not assessed. The study by Galindo et al. (20) using the FreeStyle Libre system showed an overall MARD of 14.8%, but the MARD increased to 28% with glucose levels of 2.8–3.8 mmol/L (51–69 mg/dL), which would not be acceptable. Yet the technology continues to advance, and the newest FreeStyle Libre system has a MARD similar to the Dexcom G6 (21).

In terms of hypoglycemia reduction and glycemic control, Singh et al. (22) noted in an interim report that when using a glucose telemetry system, CGM compared with point-of-care testing (with masked CGM) reduced hypoglycemia <3.9 mmol/L (70 mg/dL) and <3.0 mmol/L (54 mg/dL) measured with both blood and CGM glucose. Fortmann et al. (23) showed that CGM resulted in lower glucose levels compared with standard care with blinded CGM in a community hospital. However, in that study no differences in hypoglycemia were shown, as glucose levels were generally quite high and hypoglycemia rates were low (23).

Feasibility of CGM for COVID-19 patients has also recently been established. Shehav-Zaltzman et al. (24), using a Medtronic sensor, reported in a pilot trial that CGM data could be transferred to remote monitoring stations. Also recently reported, using the Dexcom system, Reutrakul et al. showed acceptance by nursing staff (18). While PPE use was not quantified in this report, these authors placed the sensor receiver at the patient's door (instead of at the bedside) and speculated that this technology could incorporate a true telemetry system with alarms (18). This suggests it is possible for this technology to safely manage glycemia while at the same time reducing PPE use.

What do these studies teach us, and how do we move forward?

First, these initial studies conducted outside of the ICU are encouraging, but more data are needed. It must be recalled that as of now no CGM is approved by the U.S. Food and Drug Administration (FDA) and all need to be used as adjunctive devices in the hospital. On 1 April 2020, the FDA noted that CGM could be "allowed" with the hope that remote continuous glucose data could reduce PPE and health care provider exposure (25). To date, these are goals we hope are achievable, but definitive conclusions would be premature.

Second, as data accumulate that CGM data in the hospital are adequate to assist in glycemic management, how is this extrapolated to the hundreds of hospitals, each with its own protocols? With CGM use we hope to see improvement in glucose control and less PPE utilization for patients with COVID-19; however, the challenge of using CGM in the hospital setting without a dedicated diabetes team or endocrinologist familiar with the technology will be limiting. Furthermore, even for those comfortable with the technology, currently there are no standardized inpatient protocols to address both alerts and predictive alerts. We require evidenced-based protocols on how to best advise nursing staff to respond to glucose and glucose trends.

Third, none of these recent studies examined CGM use in the ICU. The concern is that with hemodynamic changes, pressor use, and potential interfering medications, this technology will not be helpful. We anxiously await these data for this population.

Finally, and most importantly, what are our glucose targets? Would lower glucose levels without hypoglycemia benefit hospitalized patients with or without COVID-19? Based on the American Diabetes Association's *Standards of Medical Care in Diabetes*, glucose targets are recommended to be 7.8–10.0 mmol/L (140–180 mg/dL) (26), but a close examination of Fig. 1 reveals we do not know if near-normal glycemia in the hospital will improve outcomes. Certainly, the current targets will result in less hypoglycemia than was experienced by the intensive therapy groups studied in the previous randomized trials (8–12). It appears we now have the technology to definitively answer the inpatient "glucose hypothesis" question not answerable over a decade ago. The need to revisit this important question is only more urgent in the COVID-19 era.

The future of CGM in the hospital looks bright, but we are anxious for more data to be generated.

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