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

Nicole Ehrhardt and Irl B. Hirsch

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 HbA1c, 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 back 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 Critical Illness: 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
were hyperglycemia, 39% of the glucose levels patients with diabetes or uncontrolled
in the report by Bode et al. (16), in 184
areas for those infected with COVID-19.
Hospitals in both the ICU and non-ICU
care.diabetesjournals.org Ehrhardt and Hirsch 2629
improve outcomes.
fi
more safely and effectively, without de-
outcomes.
fi
primum non nocere
functions data that near-normal glycemia will
Overall, the recent reports published
of Volume Substitution and Insulin Therapy in Severe Sepsis.
—
C. "Primium non nocere" has become "give
insulin but at all costs avoid hypoglycemia." Th
of Volume Substitution and Insulin Therapy in Severe Sepsis.
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
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." Th
has been a bolus of recent reports on CGM
in the hospital. The need to minimize
PPE use and reduce exposure has ac-
erated reporting on these studies as the
goal is to manage glucose remotely, even
more safely and effectively, without defi-
nitive 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 pa-
ents 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 im-
proved 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 hypoglyce-
mia <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 differ-
ces in hypoglycemia were shown, as
 glucose levels were generally quite
high and hypoglycemia rates were low (23).
Feasibility of CGM for COVID-19 pa-
tients has also recently been established.
Shehav-Zaltzman et al. (24), using a Med-
tronic sensor, reported in a pilot trial that
CGM data could be transferred to remote
monitoring stations. Also recently re-
ported, using the Dexcom system, Reu-
trakul et al. showed acceptance by nursing
staff (18). While PPE use was not quan-
tified 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 tech-
nology 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 conclu-
sions 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 hospi-
tals, 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 hos-
pital setting without a dedicated dia-
betes team or endocrinologist familiar with
the technology will be limiting. Further-
more, even for those comfortable with
the technology, currently there are no
standardized inpatient protocols to ad-
dress both alerts and predictive alerts.
We require evidenced-based protocols
on how to best advise nursing staff to
respond to glucose and glucose trends.

| Reference/ | Total | Delta | Ratio severe |
| year/ | participants | change | hypoglycemia, |
| number | in mean glucose, | in mean glucose, intervention | intervention |
| sites | intervention arm | intervention vs. | vs. control |
| arm (n) | % diabetes | control (mg/dL) | control |
| (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 | 29% DM | 29 | 13.6 |

+ early termination of study due to hypoglycemia

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

Duality of Interest. N.E has an investigator-initiated grant with Dexcom and participated in a focus group for Novo Nordisk. I.B.H. receives grant support from Medtronic Diabetes and is on advisory boards for Abbott and Insulet and is on advisory boards for Abbott. No other potential conflicts of interest relevant to this article were reported.

References
6. Agarwal S, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission 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.