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Management of dysglycemia in critically ill adults: current evidence, clinical practice and future directions

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ABSTRACT

Hyperglycemia is among the most common metabolic disturbances in critically ill patients, affecting up to 50% of adults admitted to intensive care units (ICUs), regardless of pre-existing diabetes. Both diabetes and stress-induced hyperglycemia are associated with increased risk of organ dysfunction, healthcare-associated infections, prolonged mechanical ventilation, longer ICU and hospital length of stay, and mortality. Clinical guidelines recommend initiating intravenous insulin therapy when blood glucose remains ≥180 mg/dL (10.0 mmol/L) and targeting 140–180 mg/dL (7.8–10.0 mmol/L) for most critically ill adults. Recent advances in continuous glucose monitoring, computerized insulin dosing algorithms, automated insulin delivery systems and artificial intelligence-enabled clinical decision support are transforming glucose management in the ICU and have the potential to improve safety and efficiency. This review summarizes current understanding of the pathophysiology of stress hyperglycemia, the clinical consequences of dysglycemia, contemporary glucose targets, insulin therapy and glucose monitoring strategies. We also highlight emerging technologies, special patient populations and future directions expected to shape precision glycemic management for critically ill adults.

INTRODUCTION

Hyperglycemia is a common manifestation of critical illness and a significant, modifiable metabolic abnormality in the intensive care unit (ICU). Approximately 30%–40% of critically ill adults have pre-existing diabetes mellitus, and another 20%–40% develop transient stress-induced hyperglycemia even without a history of diabetes.[1 2] Hyperglycemia during acute illness results from a complex interplay of neuroendocrine activation, systemic inflammation, insulin resistance, altered hepatic glucose metabolism and progressive β-cell dysfunction.[3 4] Elevated glucose levels impair innate and adaptive immune function, promote endothelial dysfunction and oxidative stress, increase inflammatory cytokine production, activate prothrombotic pathways and contribute to mitochondrial dysfunction and multiorgan failure.[5–7] These mechanisms explain the consistent association between dysglycemia and poor clinical outcomes in critically ill patients, including sepsis, respiratory failure, stroke, heart attacks and postoperative care.

The optimal management of hyperglycemia in critically ill patients has evolved markedly over the past two decades. Before 2000, intensive glucose control in the ICU received little emphasis, and mean glucose levels were often kept in the low to mid-200 mg/dL range.[8] Early enthusiasm for intensive insulin therapy followed the landmark 2001 Leuven Surgical ICU trial, which demonstrated significant reductions in mortality and complications among surgical ICU patients treated to maintain blood glucose between 80 and 110 mg/dL. Additional multicenter randomized trials failed to replicate the benefits of intensive glucose control and instead showed increased rates of severe hypoglycemia.[9–13] These reports fundamentally altered clinical practice and shifted the focus towards safer, moderate glucose targets that balance the benefits of reducing severe hyperglycemia with the need to minimize iatrogenic hypoglycemia.

Technological advances are also transforming inpatient diabetes management. Continuous glucose monitoring (CGM), once used primarily in outpatient care, now shows promising accuracy and feasibility in critically ill patients. These systems provide near-CGM, help detect hypoglycemia early, reduce exposure to communicable pathogens and nursing workload by minimizing the need for frequent

tests and enable remote monitoring.[13–15] In addition, computerized insulin-dosing algorithms, predictive analytics and hybrid closed-loop systems show promise for improving glycemic control and reducing the risk of hypoglycemia. Integrating these tools with electronic health records and artificial intelligence (AI)-driven clinical decision support could revolutionize glycemic management in

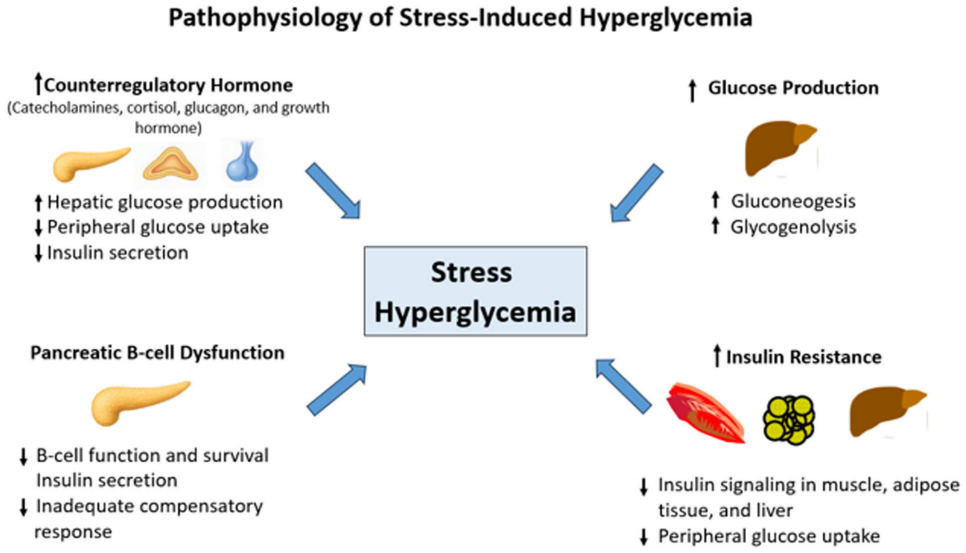


Figure 1 Pathophysiology of stress hyperglycemia. This illustration shows how, during critical illness, activation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system leads to increased secretion of catecholamines, cortisol, glucagon and growth hormone. These hormonal changes, along with inflammatory cytokines, stimulate processes such as hepatic gluconeogenesis, glycogen breakdown, peripheral insulin resistance, endothelial dysfunction, oxidative stress and immune imbalance. All of these effects contribute to stress hyperglycemia and organ failure.

future ICUs.[16–20] As critical care advances towards precision medicine, glycemic strategies are expected to shift from a uniform approach to personalized methods that account for patient-specific factors, physiology and real-time glucose monitoring.

This review provides an overview of the current understanding of the pathophysiology of stress hyperglycemia, its clinical implications, contemporary glycemic goals, glucose monitoring techniques and insulin therapies for critically ill adults. It also covers recent advances in diabetes technology, management strategies for special populations and emerging research trends likely to influence future glycemic management in the ICU.

Pathophysiology of stress hyperglycemia

Stress hyperglycemia results from a complex interplay of neuroendocrine activation, systemic inflammation, insulin resistance, increased hepatic glucose production and impaired β-cell function.[3 21] Although transient hyperglycemia may initially be an adaptive response to acute illness, persistent hyperglycemia contributes to immune dysfunction, endothelial injury, oxidative stress, mitochondrial dysfunction and multiple organ failure.[22 23] The development of stress hyperglycemia reflects the combined effects of increased endogenous glucose production and reduced peripheral glucose utilization (figure 1).

Under normal physiological conditions, insulin suppresses hepatic gluconeogenesis while promoting glucose uptake by skeletal muscle and adipose tissue.[12 24] During critical illness, these regulatory mechanisms become profoundly disrupted. Hepatic glucose production increases through both glycogenolysis and gluconeogenesis. Skeletal muscle, the principal site of insulin-mediated glucose disposal, develops marked insulin resistance, reducing glucose uptake despite elevated circulating insulin concentrations. Adipose tissue also becomes insulin-resistant, resulting in uncontrolled lipolysis and the release of free fatty acids, which further impair insulin signaling through lipotoxic mechanisms.[3 25] In addition to peripheral insulin resistance, pancreatic β-cell dysfunction develops during severe illnesses. Cytokine-mediated inflammation, oxidative stress, ischemia and glucotoxicity impair insulin secretion, especially in patients with pre-existing diabetes or impaired glucose tolerance.[26] Consequently, both insulin deficiency and insulin resistance contribute to stress hyperglycemia.

Critical illness activates the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, leading to a marked increase in circulating counter-regulatory hormones (catecholamines, cortisol, glucagon and growth hormone). These counter-regulatory hormones act synergistically to oppose insulin's actions and redirect metabolism toward glucose production and substrate mobilization.[23 27] Catecholamines stimulate hepatic glycogenolysis and gluconeogenesis, inhibit pancreatic insulin secretion through α-adrenergic mechanisms and reduce insulin-mediated glucose uptake in skeletal muscle and adipose tissue. Epinephrine also promotes lipolysis, increasing circulating free fatty acids that further impair insulin signaling and serve as substrates for hepatic glucose production. Cortisol amplifies insulin resistance by suppressing insulin receptor signaling, reducing translocation of glucose transporter type 4 in skeletal muscle, and increasing hepatic expression of key gluconeogenic enzymes. Glucagon, whose secretion

rises during acute illness despite hyperglycemia, further stimulates hepatic glucose output by activating both glycogenolysis and gluconeogenesis. Simultaneously, growth hormone reduces peripheral glucose uptake and promotes lipolysis, thereby reinforcing insulin resistance. Collectively, these hormonal adaptations ensure a continuous supply of glucose during physiological stress and also produce sustained hyperglycemia when critical illness is prolonged.[23 27]

The inflammatory response is a major driver of stress hyperglycemia, mediated by proinflammatory cytokines such as tumor necrosis factor-α, interleukin-1β, IL-6, interferon-γ and numerous chemokines.[4 25] These mediators profoundly alter glucose metabolism at both the cellular and systemic levels. Cytokines also suppress glycogen synthesis and increase hepatic glucose production, further contributing to hyperglycemia and insulin resistance.[25 28] Reactive oxygen species generated during oxidative stress amplify these signaling pathways, promoting endothelial injury, mitochondrial dysfunction and apoptosis. Importantly, insulin resistance develops rapidly during critical illness and may persist well beyond resolution of the acute event, particularly among patients with obesity or pre-existing metabolic dysfunction.

Clinical consequences of dysglycemia

Dysglycemia, including hyperglycemia, hypoglycemia and excessive glycemic variability, is a common feature of critical illness and consistently associated with adverse clinical outcomes across a broad spectrum of ICU populations.[4 29] Although hyperglycemia was historically considered an adaptive response that ensured adequate glucose availability during acute stress, extensive observational and interventional studies have demonstrated that persistent hyperglycemia is associated with increased morbidity, prolonged hospitalization and mortality.[23 27] The benefits of glycemic control must always be balanced against the risk of hypoglycemia, which remains the principal complication of insulin therapy in critically ill patients.

Hyperglycemia has been associated with poor outcomes across virtually every category of critically ill patients, including those with sepsis, trauma, acute myocardial infarction, stroke, burns, major surgery, respiratory failure and neurological injury. Numerous observational studies have shown that higher blood glucose levels are independently associated with increased mortality, longer ICU and hospital lengths of stay, longer mechanical ventilation duration and higher healthcare costs.[1 2 24] Several mechanisms contribute to these adverse effects.[4 24] Acute hyperglycemia impairs innate and adaptive immune function by reducing neutrophil chemotaxis, phagocytosis, complement activation and intracellular bacterial killing.[30] Hyperglycemia also suppresses lymphocyte proliferation and alters macrophage function, increasing susceptibility to nosocomial infections and delaying wound healing. Consequently, critically ill patients with poorly controlled glucose have higher rates of ventilator-associated pneumonia, bloodstream infections, urinary tract infections and surgical site infections.[6 13 31]

At the vascular level, hyperglycemia causes endothelial dysfunction by increasing oxidative stress, activating protein kinase C, producing advanced glycation end products and reducing nitric oxide availability.[32] These abnormalities impair microvascular blood flow, increase vascular permeability, activate coagulation pathways and promote leukocyte adhesion, leading to tissue hypoxia and multiple organ failure.[3] Importantly, the adverse effects of hyperglycemia appear to differ between patients with and without pre-existing diabetes. Multiple observational studies indicate that acute stress hyperglycemia poses a higher relative risk of death in individuals without known diabetes than in those with established diabetes.[1 2 4] Patients with chronic hyperglycemia might develop adaptive cellular mechanisms that mitigate the toxic effects of sudden glucose spikes, whereas acute hyperglycemia in previously normoglycemic individuals may indicate significant physiological stress and severe illness.[22 23]

While most clinical trials have focused on mean blood glucose concentrations, growing evidence indicates that glycemic variability is an independent determinant of adverse outcomes in critically ill patients. Glycemic variability reflects fluctuations in glucose concentrations over time and is commonly assessed using the SD, coefficient of variation, mean amplitude of glycemic excursions or CGM-derived metrics.[33–35] Acute glucose fluctuations appear to induce greater oxidative stress than sustained hyperglycemia alone. Experimental studies have demonstrated that intermittent hyperglycemia produces more pronounced endothelial dysfunction, inflammatory activation and mitochondrial injury than stable elevations in glucose concentration. Clinical studies have consistently shown associations between increased glycemic variability and ICU mortality, prolonged mechanical ventilation, multiple organ failure and longer hospital stays.[35 36] In addition, the stress hyperglycemia ratio (SHR), which adjusts admission glucose based on chronic glycemic control via glycated hemoglobin (HbA1c), appears to provide superior prognostic information compared with admission glucose alone and may help differentiate acute metabolic stress from chronic hyperglycemia.[27 37]

As with hyperglycemia, severe hypoglycemia is associated with increased mortality, whether it results directly from insulin treatment or reflects underlying disease severity. Hypoglycemia activates the sympathoadrenal system, increasing circulating catecholamines that promote tachycardia, hypertension, myocardial ischemia and ventricular arrhythmias. In the central nervous system, glucose deprivation impairs neuronal function and may lead to seizures, coma or permanent neurological injury.[38] Critically ill patients are particularly vulnerable because they frequently lack the ability to recognize or communicate symptoms of hypoglycemia, especially when sedated or mechanically ventilated. Large,

randomized trials evaluating intensive insulin therapy consistently demonstrated substantially higher rates of severe hypoglycemia than moderate glycemic control, providing one of the major reasons for abandoning intensive glucose normalization as routine ICU practice.[39 40] Consequently, preventing hypoglycemia has become a central objective of contemporary glycemic management strategies and is considered equally important to treating hyperglycemia.[29]

Glycemic targets in critically ill adults

The optimal glycemic target for critically ill patients has remained one of the most debated topics in critical care medicine. While observational studies consistently show an association between hyperglycemia and adverse clinical outcomes, randomized clinical trials have failed to show that blood glucose normalization improves survival across heterogeneous ICU populations.[6 13] Instead, accumulating evidence indicates that the benefits of reducing hyperglycemia must be carefully balanced against the increased risk of hypoglycemia associated with intensive insulin therapy.[9 11 39] Consequently, contemporary glycemic management has evolved from a strategy focused on strict glucose normalization toward a more individualized approach that emphasizes moderate glycemic control, avoidance of hypoglycemia and minimization of glycemic variability.[29]

The modern era of inpatient glycemic management began with the landmark Leuven Surgical Intensive Care Unit study published by Van den Berghe and colleagues in 2001.[41] In this single-center randomized trial involving predominantly postoperative cardiac surgery patients, intensive insulin therapy targeting blood glucose concentrations between 80 and 110 mg/dL (4.4–6.1 mmol/L) significantly reduced ICU mortality by 42%, decreased bloodstream infections, acute kidney injury requiring dialysis, critical illness polyneuropathy, duration of mechanical ventilation and length of ICU stay. These remarkable findings generated widespread enthusiasm for intensive insulin therapy and led many institutions to adopt protocols targeting near-normal glucose concentrations. However, subsequent studies failed to consistently reproduce these results. The Leuven Medical ICU trial demonstrated reduced morbidity but no significant reduction in overall mortality, except among patients requiring prolonged ICU care.[31 42] Similarly, other trials were terminated prematurely because of concerns regarding severe hypoglycemia and failure to demonstrate clear clinical benefit.[13] Subsequent studies highlighted the challenges of implementing intensive insulin therapy across diverse ICU populations and emphasized the importance of balancing efficacy with safety[43] (table 1).

Current guideline recommendations

Current international guidelines are remarkably consistent in the management of hyperglycemia in critically ill patients. Intravenous insulin infusion is the preferred treatment because of its rapid onset, predictable pharmacokinetics and ability to meet the rapidly changing metabolic needs of critical illness.[29] The Society of Critical Care Medicine guidelines recommend initiating insulin therapy for persistent blood glucose concentrations ≥180 mg/dL (10.0 mmol/L) and targeting a glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) for most critically ill adults.[44] Similarly, the American Diabetes Association, the American Association of Clinical Endocrinology and the Joint British Diabetes Societies recommend initiating insulin therapy when blood glucose remains persistently above 180 mg/dL and maintaining it between 140 and 180 mg/dL (7.8–10.0 mmol/L) during critical illness.[29 45] These recommendations emphasize protocol-driven insulin administration, frequent glucose monitoring and avoidance of hypoglycemia as the primary objectives of inpatient glycemic management.

Although a blood glucose target of 140–180 mg/dL (7.8–10.0 mmol/L) is appropriate for most critically ill patients, increasing evidence suggests that a single glycemic target may not be optimal for all ICU populations.[46] The impact of dysglycemia on clinical outcomes appears to depend on several patient-specific factors, including pre-existing diabetes, antecedent glycemic control, illness severity, nutritional status and the underlying diagnosis. As a result, interest has grown in developing more individualized approaches to glycemic management. Patients with long-standing diabetes are chronically exposed to elevated glucose concentrations and may, therefore, be more tolerant of hyperglycemia than patients without diabetes. Consistent with this concept, observational studies have shown that hyperglycemia is associated with a greater increase in mortality risk among patients without diabetes than among those with established diabetes.[1 7 47 48] At the same time, lowering glucose too aggressively in patients with chronic hyperglycemia may have unintended consequences. Because these patients adapt to persistently elevated glucose levels, glucose concentrations that are considered normal may be perceived physiologically as hypoglycemic, a phenomenon known as relative hypoglycemia, which may trigger sympathetic activation, cardiovascular instability and other adverse effects.[37]

Glycemic monitoring-beyond mean glucose

Accurate glucose monitoring is fundamental to the safe and effective management of hyperglycemia in critically ill patients. Unlike in ambulatory diabetes care, where glucose concentrations are relatively stable, critically ill patients experience rapid fluctuations due to changes in illness severity, vasopressor requirements, nutritional support, corticosteroid therapy, renal function and insulin sensitivity.[14 36] Consequently, glucose monitoring in the ICU must provide timely, accurate and actionable information that supports safe insulin titration while minimizing the risks of both hyperglycemia and hypoglycemia. Advances in CGM and computerized decision support are expanding the capabilities of glucose assessment; however, POC blood glucose testing remains the

Table 1 Randomized clinical trials of intensive insulin therapy in critically ill patients

Trial	Setting (# Pts, n)	BG target (mg/dL)	Primary outcome	Rate of outcome	OR (95% CI)	P value mortality
Leuven SICU 2001[41]	SICU (n: 1548)	IIT: 80–110 CON: <215	ICU mortality	IIT: 4.6 CON: 8.0	0.58 (0.38 to 0.78)	<0.04
Leuven MICU 2006[31]	MICU (n: 1200)	IIT: 80–110 CON: <215	Hospital mortality	IIT: 27.3 CON: 40.0	0.94 (0.84 to 1.06)	N.S.
GLUCONTROL 2007[11]	ICU (n: 101)	IIT: 80–110 CON: 140–180	ICU mortality	IIT: 16.7 CON: 15.2	1.10 (0.84 to 1.44)	N.S.
VISEP 2008[93]	ICU (n: 537)	IIT: 80–110 CON: 180–200	28-day mortality	IIT: 24.7 CON: 26.0	0.95 (0.70 to 1.28)	N.S.
De La Rosa 2008[94]	SICU/MICU (n: 504)	IIT: 80–110 CON: 180–200	28-day mortality	IIT: 36.6 CON: 32.4	1.1 (0.85 to 1.42)	N.S.
Arabi 2008[95]	SICU/MICU (n: 523)	IIT: 80–110 CON: 180–200	ICU mortality	IIT: 13.5 CON: 17.1	1.09 (0.70 to 1.72)	N.S.
NICE-SUGAR 2009[9]	ICU (n: 6104)	IIT: 81–108 CON: 144–180	90-day mortality	IIT: 27.5 CON: 24.9	1.14 (1.02 to 1.28)	0.02
GLUCO-CABG 2015[96]	SICU (n: 301)	IIT: 100 CON: 140	Hospital complications*	IIT: 42 CON: 52	0.67 (0.43 to 1.06)	N.S.
CONTROLLING 2021[97]	SICU/MICU (n: 2075)	Individualized based on HbA1c CON: 180	90-day mortality	Intervention: 32.8 CON: 30.5	1.1 (0.97 to 1.36)	N.S.
LUCID 2022[98]	MICU/SICU	Liberal: 180–252 CON: 108–180	Hypoglycemia<72†	Liberal: 5% CON: 18%	0.21 (0.09 to 0.49)	N.S.
TGC-fast 2023[99]	SICU/MICU (n: 9230)	IIT: 80–110 CON: <215	ICU mortality	ITT: 5.8 CON: 5.3	1.00 (0.96 to 1.04)	N.S.

*GLUCO-CABG: primary outcome was differences in a composite of hospital complications including mortality, wound infection, pneumonia, bacteremia, respiratory failure, acute kidney injury and major cardiovascular events.
†LUCID: the primary outcome was incident hypoglycemia (<72 mg/dL).
CON, control group; HbA1c, glycated hemoglobin; ICU, intensive care unit; IIT, intensive insulin therapy; MICU, medical ICU; N.S, not significant; SICU, surgical ICU.

current Food and Drug Administration-approved standard of care in most ICUs.

The primary objectives of glucose monitoring in critically ill patients are to (1) identify persistent hyperglycemia requiring insulin therapy, (2) guide IV insulin dose adjustments, (3) detect impending or established hypoglycemia and (4) assess overall glycemic control throughout the ICU stay.[36] Because critically ill patients often have rapidly changing insulin requirements, glucose measurements must be performed frequently and interpreted within the context of ongoing changes in clinical status, nutrition, medications and organ function. Errors in glucose measurement may lead to inappropriate insulin dose adjustments and contribute to severe hypoglycemia or persistent hyperglycemia.[49]

POC blood glucose testing

POC capillary glucose testing using handheld glucometers remains the most widely used method for glucose monitoring in hospitalized patients because it is inexpensive, rapid and readily available. In non-critically ill patients, capillary POC testing generally provides acceptable accuracy for routine insulin administration. However, several physiological disturbances common in critically ill patients may substantially reduce its reliability. Peripheral hypoperfusion resulting from shock, vasopressor therapy, hypothermia or severe edema reduces capillary blood flow and may produce falsely elevated glucose readings.[49] Similarly, anemia, polycythemia, hypoxemia, acid–base disturbances and interfering medications such as acetaminophen, dopamine, mannitol, ascorbic acid or maltose-containing solutions may affect the analytical performance of some glucose meters.[50] Consequently, reliance on capillary glucose measurements in unstable ICU patients may lead to inappropriate insulin dosing and increased risk of hypoglycemia, or missed hyperglycemia.

Venous plasma glucose measured in the central laboratory is the reference standard for glucose determination. However, the longer turnaround time for laboratory analysis limits its usefulness for real-time insulin titration. Therefore, laboratory glucose measurements are primarily used to confirm unexpected POC values or to calibrate monitoring systems, rather than to directly adjust routine insulin doses. Arterial blood sampling via indwelling arterial catheters is the preferred method for glucose monitoring during intravenous insulin infusion

because it offers greater analytical accuracy and minimizes many of the physiological limitations associated with capillary sampling.[46 51] Several studies have reported that arterial glucose measurements correlate more closely with central laboratory plasma glucose values than capillary measurements, particularly among patients receiving vasopressor therapy or experiencing circulatory shock. Consequently, arterial sampling is recommended whenever arterial access is available and patients are receiving intravenous insulin infusion.[51 52]

The frequency of glucose monitoring should reflect the patient's metabolic stability and the intensity of insulin therapy. During initiation of intravenous insulin infusion or periods of rapidly changing insulin requirements, blood glucose should generally be measured hourly until stable glycemic control is achieved. Once glucose concentrations remain within the target range and insulin requirements become relatively stable, monitoring intervals may be extended to every 2–4 hours, according to institutional protocols.[3 53] The 2024 Society of Critical care Medicine guidelines recommend glucose assessment at intervals of no more than 1 hour during periods of glycemic instability or when intravenous insulin infusion rates are being actively adjusted.[46] Frequent monitoring is particularly important during initiation or interruption of enteral or parenteral nutrition, changes in corticosteroid dosing, initiation of renal replacement therapy and transition from intravenous to subcutaneous insulin, all of which are associated with substantial changes in insulin requirements.[46 54]

Continuous glucose monitoring

CGM represents one of the most significant technological advances in inpatient diabetes care. Modern CGM systems measure interstitial glucose concentrations every 1 to 5 min, providing nearly continuous assessment of glucose trends, the direction of change and glycemic variability. Unlike intermittent POC testing, CGM allows early detection of impending hypoglycemia and hyperglycemia, enabling proactive insulin adjustments before clinically significant dysglycemia develops.[36 55]

Initial studies evaluating CGM in critically ill patients reported variable accuracy because of impaired tissue perfusion, edema, vasopressor therapy and sensor calibration requirements. However, newer generation sensors have demonstrated substantial improvements in analytical performance, with mean absolute relative difference values generally ranging from 10% to 14%, and over 98% of paired glucose values falling within clinically acceptable error grid zones.[56 57] Recent randomized trials have demonstrated that CGM detects substantially more episodes of asymptomatic and nocturnal hypoglycemia than conventional POC testing while providing detailed information regarding glycemic variability and time in range.[14 56 58] Early recognition of declining glucose concentrations allows clinicians to reduce insulin infusion rates or administer carbohydrates before severe hypoglycemia develops.[59 60] This capability is particularly important in mechanically ventilated or sedated patients who cannot recognize or report symptoms.

During the COVID-19 pandemic, the widespread adoption of CGM among hospitalized patients demonstrated additional benefits, including reduced healthcare worker exposure, decreased use of personal protective equipment and fewer bedside fingerstick glucose measurements.[14 61 62] Despite these advances, several limitations currently preclude routine replacement of POC glucose testing. Physiological lag between plasma and interstitial glucose becomes clinically relevant during periods of rapidly changing glucose concentrations, such as the initiation of an insulin infusion or treatment of hypoglycemia.[36] Sensor accuracy may also be affected by poor tissue perfusion, severe edema, acetaminophen administration and compression artifacts. Consequently, most professional societies currently recommend using CGM as an adjunct rather than a replacement for standard glucose monitoring in critically ill patients.

Insulin therapy in critically ill adults

Continuous intravenous insulin infusion remains the gold standard for treating hyperglycemia in critically ill adults because it provides predictable pharmacokinetics, rapid titration and superior adaptability to the rapidly changing metabolic conditions of critical illness. Standardized nurse-driven or computerized insulin protocols, combined with frequent glucose monitoring and multidisciplinary quality improvement initiatives, allow safe achievement of recommended glycemic targets while minimizing hypoglycemia (figure 2).

Based on current evidence, a pragmatic approach to glycemic management in critically ill adults includes[29 46]:

1. Initiate intravenous insulin therapy for persistent blood glucose concentrations ≥180 mg/dL (10.0 mmol/L).
2. Target a glucose range of 140–180 mg/dL for most critically ill patients.
3. Avoid severe hypoglycemia (<70 mg/dL) by using standardized insulin protocols, frequent glucose monitoring and timely adjustments to insulin infusion rates.
4. Consider lower glucose targets (110–140 mg/dL) only in carefully selected patients when these can be achieved safely by experienced teams using validated protocols with minimal hypoglycemia.
5. Recognize that glycemic variability, time in range and antecedent glycemic control may influence prognosis and are likely to become increasingly important components of individualized glycemic management.

Intravenous insulin infusion remains the cornerstone of glycemic management in critically ill patients because of its rapid onset of action, short half-life and ease of titration in response to rapidly changing metabolic demands. Unlike subcutaneous insulin, which is affected by tissue perfusion, edema, vasopressor therapy and variable absorption, continuous intravenous insulin provides predictable pharmacokinetics, allowing precise adjustment of insulin delivery in response to dynamic changes in blood glucose, nutritional support, organ

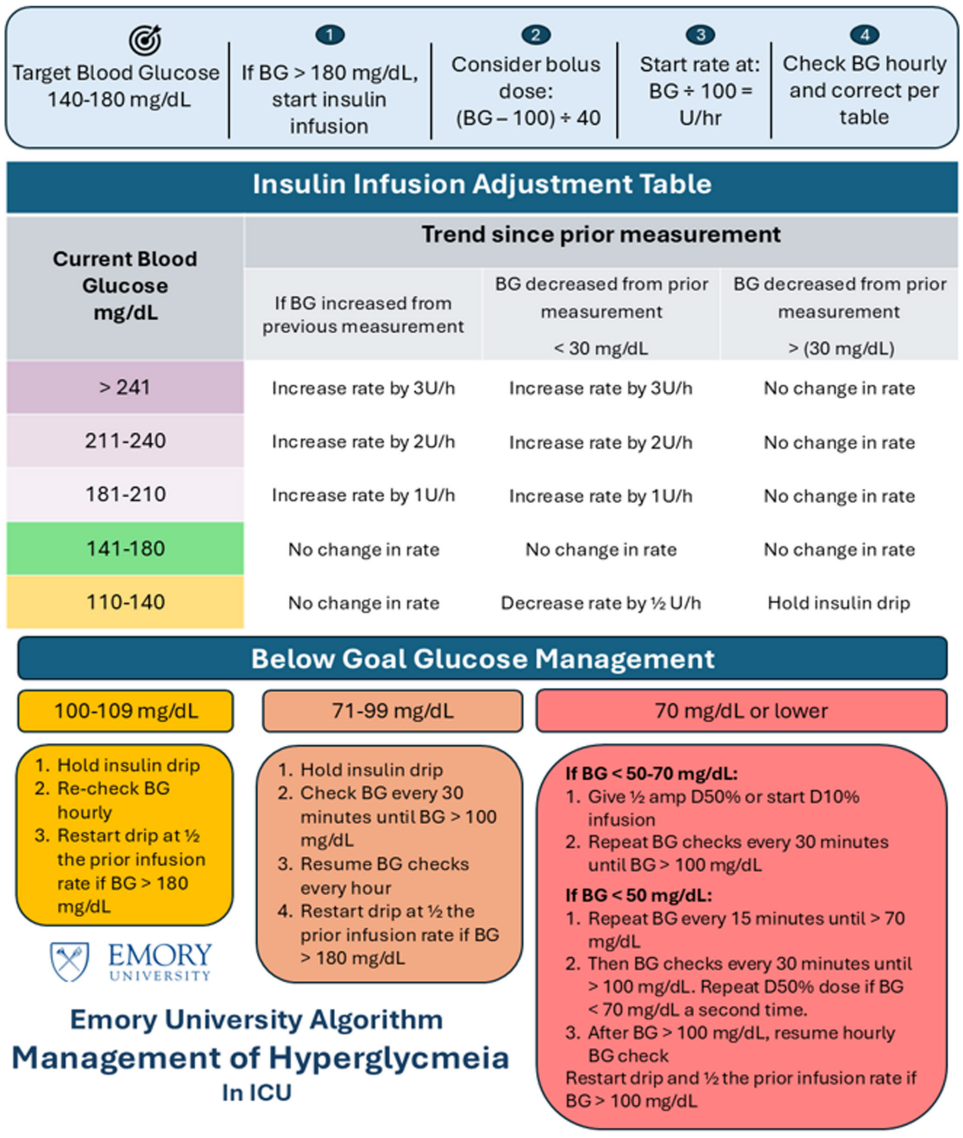


Figure 2 Emory University Glucose Management in the ICU settings. Emory University ICU Hyperglycemia Management Algorithm for intravenous insulin infusion therapy. The target blood glucose (BG) range is 140–180 mg/dL. Hourly BG measurements guide infusion rate adjustments based on the current glucose level and the direction and magnitude of change from the prior measurement.

function and illness severity. The plasma half-life of intravenously administered insulin is approximately 5–10 min, allowing rapid attainment of steady-state concentrations and an equally rapid reduction in insulin delivery when glucose concentrations decline. This pharmacokinetic profile enables clinicians to respond promptly to changes in nutritional intake, corticosteroid administration, renal replacement therapy, vasopressor requirements or resolution of systemic inflammation.

During the past two decades, numerous algorithms have been developed, differing in how they initiate insulin, calculate dose adjustments, incorporate prior glucose values and respond to changes in insulin sensitivity.[6 63–65] Effective insulin algorithms incorporate not only the current glucose concentration but also the rate of change in glucose, the current insulin infusion rate and the patient's recent response to therapy. Algorithms that adjust insulin doses solely based on the most recent glucose measurement are less effective because they fail to account for rapidly changing insulin requirements during critical illness.

Several clinical situations warrant immediate initiation of intravenous insulin irrespective of the degree of hyperglycemia. These include diabetic ketoacidosis, hyperosmolar hyperglycemic state, perioperative management following cardiac surgery, severe burns, organ transplantation and patients receiving high-dose vasopressor support or extracorporeal therapies. In these settings, continuous insulin infusion facilitates rapid metabolic stabilization while allowing frequent dose adjustments according to evolving clinical conditions.

In most ICUs, insulin infusion protocols are implemented primarily by bedside nurses using predefined adjustment algorithms.[29] This approach has several advantages. First, nurses can respond immediately to changes in glucose concentrations without waiting for physician orders, thereby reducing treatment delays. Second, standardized protocols reduce interprovider variability and improve consistency of care across shifts and clinical teams. Finally, nurse-driven algorithms decrease cognitive workload and facilitate adherence to evidence-based practice.[29]

The increasing complexity of glucose management has stimulated the development of computerized insulin dosing systems that automate insulin dosing recommendations using validated mathematical algorithms.[66] These systems integrate current and previous glucose measurements, insulin infusion rates and glucose trends to generate individualized insulin adjustments. Several randomized studies have demonstrated that computerized algorithms reduce the time required to reach target glucose concentrations, increase time spent within the desired glucose range, decrease glycemic variability and reduce the incidence of severe hypoglycemia compared with conventional paper-based protocols.[66–68] Additional advantages include elimination of manual calculation errors, standardized implementation across institutions and continuous quality monitoring. Although computerized decision support has shown considerable promise, widespread implementation remains limited by integration challenges with electronic health records, institutional costs and the need for ongoing technical support. Nevertheless, computerized insulin dosing is expected to become increasingly common as hospitals continue to digitize critical care workflows.

Current evidence supports initiating intravenous insulin therapy for persistent blood glucose concentrations ≥180 mg/dL (10.0 mmol/L) in critically ill patients.[46] Treatment decisions should be based on confirmed, sustained hyperglycemia rather than isolated glucose elevations. Once intravenous insulin is initiated, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most ICU patients; however, glycemic targets vary across clinical societies (table 2). Frequent glucose monitoring is essential because insulin requirements can change rapidly in response to changes in illness severity, nutritional support, medications and organ function.

Current guidelines recommend hourly glucose monitoring during insulin initiation, periods of glycemic instability or after significant changes in insulin infusion rates. Once glucose concentrations remain stable within the target range, monitoring intervals may be extended to every 2–4 hours according to institutional protocols. Insulin requirements should be reassessed whenever clinical conditions change, including the initiation or discontinuation of enteral or parenteral nutrition, glucocorticoid therapy, renal replacement therapy, resolution of sepsis or withdrawal of vasopressor support. Failure to promptly adjust insulin infusion rates during these transitions is a common cause of hypoglycemia in critically ill patients.

Table 2 Clinical guidelines recommendations for target glucose levels in the ICU

Guideline	ICU
American Diabetes Association {American Diabetes Association Professional Practice Committee for, 2026 #3181}	Initiate insulin therapy for persistent hyperglycemia (glucose>180 mg/dL (10 mmol/L) Treatment goal: for most people, target a glucose level between 140 and 180 mg/dL (7.8–10.0 mmol/L) More stringent goals 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate for selected individuals (critically ill postsurgical, cardiac surgery), if achievable without significant hypoglycemia
American College of Physicians[107]	Recommends against intensive insulin therapy to normalize blood glucose in surgical/medical ICU patients with or without diabetes. Treatment goal: target glucose of 140 mg/dL (7.8–11.1 mmol/L) in insulin treated patients in surgical/medical ICU
Society of Critical Care Medicine {Honarmand, 2024 #3195}	BG>180 mg/dL should trigger insulin therapy Maintain glucose levels between 140 and 200 mg/dL (7.8–11.1 mmol/L) while avoiding hypoglycemia
Endocrine Society {Korytkowski, 2022 #3180}	Initiate insulin therapy for persistent hyperglycemia (glucose>180 mg/dL (10 mmol/L) Treatment goal: for most people, target a glucose level between 140–180 mg/dL (7.8–10.0 mmol/L)
Society of Thoracic Surgeons (Guidelines specific to adult cardiac surgery) {Lazar, 2009 #1189}	Continuous IV insulin infusion preferred over SC or intermittent intravenous boluses. Treatment goal: recommend glucose<180 mg/dL (10.0 mmol/L) during surgery
Joint British Diabetes Society for Inpatient Care {14., #3247}	Target blood glucose levels in most people of between 110 and 180 mg/dL (6.0–10 mmol/L) with an acceptable range of between 70 and 215 mg/dL (4.0–12.0 mmol/L) Perioperative target blood glucose: 110–180 mg/dL (6.0–10 mmol/L) with acceptable range up to 215 mg/dL (12 mmol/L)
American Society of Parenteral and Enteral Nutrition (ASPEN) {McMahon, 2013 #3065}	Target blood glucose goal range of 7.8–10 mmol/L in people receiving nutrition support.
Surviving Sepsis Campaign 2021{Evans, 2021 #3249}	Initiate insulin therapy for glucose>180 mg/dL (10 mmol/L) Treatment goal: for most people, target a glucose level between 140 and 180 mg/dL (7.8–10 mmol/L)

ICU, intensive care unit.

Transition from intravenous to subcutaneous insulin

Transitioning from intravenous insulin to subcutaneous insulin is a critical step in ICU management and is frequently associated with rebound hyperglycemia

when not performed appropriately. Transition should be considered once the patient is hemodynamically stable, insulin requirements have stabilized and nutritional intake is predictable.[46 69]

The daily insulin requirement can be estimated from the patient's intravenous insulin requirements during the preceding 6–12 hours. Most protocols recommend administering approximately 60%–80% of the projected 24-hour intravenous insulin requirement as the initial subcutaneous total daily dose, with approximately 50% administered as basal insulin and the remainder divided among scheduled prandial or nutritional insulin doses when oral intake or enteral feeding is established.[46 69] Patients who remain fasting or receive continuous nutritional support generally require basal insulin with scheduled correction doses.

To prevent rebound hyperglycemia, basal insulin should be administered 2–4 hours before discontinuing the insulin infusion, allowing sufficient time for subcutaneous absorption while maintaining continuous insulin availability.[69] This overlap is particularly important in patients with type 1 diabetes, in whom interruption of insulin delivery for only a few hours may precipitate diabetic ketoacidosis.[69]

Prevention and management of hypoglycemia

Hypoglycemia in hospitalized patients is generally defined as a blood glucose concentration <70 mg/dL (3.9 mmol/L), corresponding to the threshold at which physiological counterregulatory responses are activated.[29] Clinically significant hypoglycemia is typically defined as <54 mg/dL (3.0 mmol/L), while severe hypoglycemia refers to episodes associated with cognitive impairment requiring external assistance. The reported incidence of hypoglycemia varies according to ICU population, glycemic targets, insulin protocol and glucose monitoring frequency. In large, randomized trials evaluating intensive insulin therapy, severe hypoglycemia occurred in 5%–18% of patients, compared with less than 2% among patients managed using moderate glycemic targets.[15]

Hypoglycemia remains the most important complication of insulin therapy in critically ill patients and is the principal factor limiting attempts to achieve tighter glycemic control. Evidence accumulated over the past two decades has demonstrated that severe hypoglycemia is independently associated with increased mortality, prolonged ICU and hospital stay, neurological injury, cardiac arrhythmias and greater healthcare resource utilization.[15 29 70] Although the causal relationship between hypoglycemia and adverse outcomes remains incompletely understood, preventing hypoglycemia has become a central objective of contemporary glycemic management and is considered equally important as treating hyperglycemia.[29]

Acute reductions in plasma glucose activate a complex neuroendocrine counter-regulatory response characterized by increased secretion of glucagon, epinephrine, cortisol and growth hormone. These hormones promote hepatic glucose production while simultaneously increasing heart rate, blood pressure and myocardial oxygen demand. In critically ill patients, these physiological responses may become maladaptive. Excess catecholamine release can precipitate myocardial ischemia, ventricular arrhythmia and hemodynamic instability, particularly in patients with underlying cardiovascular disease. Experimental studies have demonstrated that hypoglycemia prolongs the QT interval, increases sympathetic activation, enhances platelet aggregation and promotes inflammatory and prothrombotic pathways, potentially increasing the risk of adverse cardiovascular events.[15] Even brief episodes of severe hypoglycemia have been associated with increased mortality in observational studies, although it remains uncertain whether hypoglycemia directly contributes to death or primarily reflects greater illness severity.

Hypoglycemia in critically ill patients is multifactorial and usually results from an imbalance between insulin administration and rapidly changing glucose requirements.[3 71] Unexpected interruption of enteral or parenteral nutrition is among the most common causes of hypoglycemia during intravenous insulin therapy. When insulin infusion continues despite cessation of carbohydrate delivery, blood glucose concentrations may decline rapidly. Standardized ICU protocols should, therefore, require immediate reassessment of insulin therapy whenever nutritional support is interrupted.[15] Frequent glucose monitoring remains essential. During intravenous insulin infusion, glucose should generally be measured hourly until stable glycemic control is achieved. Prompt recognition of hypoglycemia requires vigilance because critically ill patients often cannot communicate symptoms. CGM, when available, may facilitate early detection of falling glucose concentrations before severe hypoglycemia develops.

For patients with confirmed glucose concentrations <70 mg/dL, insulin infusion should be interrupted immediately while reversible causes are investigated. The intravenous administration of 25 g of dextrose (50 mL of 50% dextrose solution) remains the standard treatment for conscious or unconscious critically ill patients without enteral access.[21 72] Patients receiving enteral nutrition who are awake and able to tolerate oral intake may receive rapidly absorbed carbohydrates followed by sustained carbohydrate supplementation. Blood glucose should be reassessed approximately 15 min after treatment, with repeated dextrose administration if hypoglycemia persists. Once glucose concentrations normalize, insulin therapy should be restarted cautiously after the underlying precipitating factor is corrected. Simply restarting insulin at the previous infusion rate without reassessing insulin requirements frequently results in recurrent hypoglycemia.

Emerging diabetes technology tools

CGM, computerized insulin dosing algorithms, hybrid closed-loop systems and AI-enabled clinical decision

support offer the potential to improve both the safety and precision of inpatient glycemic management.[73 74] Although these technologies are still evolving, they represent a paradigm shift from reactive glucose management toward continuous, data-driven and increasingly automated care.

Remote glucose monitoring with CGM

One of the most important innovations enabled by CGM is remote glucose surveillance.[61 75] Modern CGM systems transmit glucose data wirelessly to centralized monitoring stations, allowing clinicians to observe glucose trends from outside patient rooms. Remote monitoring offers several additional advantages beyond infection control. Centralized glucose surveillance enables endocrine consultation teams to simultaneously monitor multiple patients, facilitates rapid identification of deteriorating glycemic control and allows earlier intervention before clinically significant dysglycemia develops. Nursing workflow may also improve by reducing the frequency of bedside fingerstick testing and enabling prioritization of patients requiring immediate attention.

The future of glucose monitoring in critical care is likely to involve integrating CGM with computerized insulin-dosing algorithms, electronic health records and AI-based clinical decision support systems. Such systems can provide automated prediction of impending dysglycemia, optimize insulin dosing, reduce nursing workload and improve overall safety. Remote glucose surveillance may further enhance ICU workflow by allowing centralized monitoring of multiple patients simultaneously and facilitating early intervention before clinically significant glucose abnormalities occur. As these technologies mature, glucose monitoring strategies will likely shift from intermittent measurement of isolated glucose values toward continuous assessment of the entire glycemic profile, including time in range, glycemic variability and predictive glucose trends.

AID systems

Automated insulin delivery (AID), or hybrid closed-loop insulin delivery, combines CGM with automated insulin infusion algorithms.[20 76] These systems continuously analyze glucose sensor values and automatically adjust insulin delivery, requiring minimal clinician intervention. Preliminary studies in hospitalized patients have shown encouraging improvements in glucose control without an increase in severe hypoglycemia.[20 77] Early pilot studies in critically ill adults suggest that AID is feasible and may reduce nursing workload while maintaining glucose concentrations within target ranges. Nevertheless, several barriers currently limit ICU implementation. Rapidly changing insulin resistance, variable nutritional support, vasopressor therapy, edema and the complexity of critical illness require algorithms that can respond appropriately to rapidly evolving physiological conditions.[19 77]

AI and predictive analytics

AI is expected to play an increasingly important role in glycemic management in critical care.[78] Machine learning algorithms can integrate continuous glucose measurements with numerous clinical variables, including nutritional intake, corticosteroid administration, vasopressor requirements, renal function, inflammatory biomarkers and illness severity, to predict future glucose concentrations and optimize insulin dosing. Unlike conventional algorithms based on predefined mathematical equations, AI systems continuously learn from individual patient responses and adapt treatment recommendations accordingly.[77] Predictive analytics may identify patients at high risk of impending hypoglycemia several hours before glucose concentrations decline, allowing proactive adjustments to insulin therapy. Beyond insulin dosing, AI may improve ICU workflow by prioritizing patients requiring immediate clinical attention, reducing alarm fatigue and supporting individualized glycemic targets based on patient-specific characteristics.

Glycemic management in special populations and clinical situations

Cardiac surgery

Several studies have demonstrated associations between postoperative hyperglycemia and increased risk of postoperative complications, including deep sternal wound infection, atrial fibrillation, extended mechanical ventilation, acute kidney injury and death.[6 79] Although initial research suggested that intensive insulin therapy could benefit cardiac surgery patients, later randomized trials have not shown improved survival with strict glucose control.[13] Current guidelines recommend keeping blood glucose levels between 140 and 180 mg/dL, avoiding both severe hyperglycemia and hypoglycemia. Since insulin needs can vary rapidly after surgery, standardized intravenous insulin protocols with frequent glucose monitoring are the mainstay of management.[47]

Acute myocardial infarction

Hyperglycemia during acute coronary syndromes is consistently associated with increased mortality regardless of diabetes status.[80] Nevertheless, intensive glucose lowering has not improved survival, and current recommendations favor maintaining glucose concentrations between 140 and 180 mg/dL while avoiding hypoglycemia, which may exacerbate myocardial ischemia and precipitate ventricular arrhythmias.[29]

Acute neurological injury

Hyperglycemia frequently occurs alongside conditions like acute ischemic stroke, intracerebral hemorrhage, traumatic brain injury and subarachnoid hemorrhage. High glucose levels can lead to increased cerebral lactate, oxidative stress, excitotoxic injury and blood–brain barrier disruption, potentially worsening neurological damage. Despite these observations, randomized trials have failed to demonstrate benefit from intensive insulin

therapy, largely because of increased hypoglycemia.[81 82] Additionally, hypoglycemia might be particularly detrimental in patients with acute brain injuries, as their cerebral glucose supply is already limited. Therefore, moderate glycemic control is the preferred approach in neurocritical care, with a focus on preventing both severe hyperglycemia and hypoglycemia. Accordingly, moderate glycemic control remains recommended for patients with acute neurological injury.[82]

Sepsis

Hyperglycemia is particularly common during sepsis because inflammatory cytokines, catecholamines, cortisol and glucagon produce profound insulin resistance and increased hepatic glucose production.[83 84] The severity of hyperglycemia parallels illness severity and correlates with circulating inflammatory mediators. Despite the strong association between hyperglycemia and mortality in septic patients, randomized trials have consistently failed to demonstrate improved survival with intensive glucose lowering. Furthermore, septic patients are especially vulnerable to hypoglycemia because insulin sensitivity may change rapidly during resolution of infection, antibiotic therapy, vasopressor withdrawal or improvement in tissue perfusion. Current guidelines, therefore, recommend standard glucose targets of 140–180 mg/dL in septic patients.[29 83 84]

Trauma and burn patients

Studies show that hyperglycemia in burn patients is associated with increased infection rates, poor wound healing, delayed skin graft acceptance and longer hospital stays.[85] However, overly aggressive glucose control can raise the risk of hypoglycemia in these unstable patients. Therefore, standardized intravenous insulin protocols, with frequent monitoring and adjustments, remain crucial.[9 39]

Nutritional support

Enteral and parenteral nutrition significantly influence inpatient glucose control.[86] Continuous enteral feeding generally produces relatively stable glucose levels but needs consistent basal insulin coverage. However, stopping enteral feeding for procedures, gastrointestinal issues or tube problems is a common cause of hypoglycemia during intravenous insulin treatment.[86 87] Any changes in nutritional delivery should trigger an immediate review of insulin needs to prevent both high and low blood sugar levels.[47]

Renal replacement therapy

Acute kidney injury and renal replacement therapy substantially alter insulin pharmacokinetics and glucose metabolism. Reduced renal clearance prolongs insulin action, while dialysis can increase insulin sensitivity and affect glucose levels by altering substrate metabolism and dialysate composition.[88] Insulin needs usually decrease as renal function worsens but can vary greatly during dialysis sessions.[75] Therefore, patients receiving continuous or intermittent renal replacement therapy must have their glucose monitored more frequently, with insulin doses tailored to their individual needs.[89]

Corticosteroid-induced hyperglycemia

Systemic glucocorticoids are among the most common causes of hospital-acquired hyperglycemia.[21 90 91] Corticosteroids increase hepatic glucose production, impair peripheral glucose uptake and cause significant insulin resistance—especially in the afternoon and evening after morning doses of intermediate-acting steroids.[92] Critically ill patients receiving high doses often need substantial increases in insulin infusion rates. Conversely, reducing or stopping corticosteroids can quickly lower insulin needs, which may lead to hypoglycemia; therefore, such patients require frequent glucose monitoring and insulin adjustments to maintain glycemic control.[29]

Future directions and research priorities

The approach to managing hyperglycemia in critically ill patients has changed significantly over the past 20 years. It has shifted from aggressive glucose normalization to safer, moderate glycemic control that prioritizes preventing hypoglycemia. However, key questions remain about optimal glucose targets, new glycemic metrics and the integration of emerging technologies into intensive care. Future studies are expected to focus on precision glycemic management, tailoring therapy to individual patient characteristics, disease severity, chronic blood sugar levels and real-time metabolic data, rather than relying on fixed glucose thresholds.

CGM is expected to play a central role in inpatient glycemic management. Improvements in sensor accuracy and connectivity have made CGM a valuable complement to POC testing, allowing ongoing monitoring of glucose trends, variability, and time in range. As more clinical trials are conducted, CGM-guided insulin therapy may become the standard approach for certain critically ill patients. Integrating CGM with automated insulin dosing algorithms has laid the foundation for systems that continuously adjust insulin infusion rates based on real-time glucose data. These hybrid closed-loop systems, already widely used in outpatient diabetes care, are among the most promising developments for managing diabetes in hospital settings.

AI and machine learning could significantly improve glycemic control in critical care. Unlike traditional insulin protocols that rely on fixed mathematical rules, AI systems analyze patient-specific data to tailor insulin recommendations to real-time physiological responses. These technologies can forecast hyperglycemia or hypoglycemia, detect shifts in insulin sensitivity and support personalized insulin dosing during critical illness. However, AI should be viewed as a decision-support tool that complements, not replaces, clinical judgment. Effective implementation requires thorough validation, transparent algorithms and seamless integration into ICU workflows.

Several important research questions remain unanswered and should be addressed in future clinical studies:

1. What level of time in range by CGM is associated with improved survival?
2. Can glycemic variability become a therapeutic target?
3. Should CGM become the standard of care in the ICU?
4. Which critically ill populations benefit most from AID systems?
5. Can AI safely automate insulin dosing?
6. Do technology-assisted approaches improve patient-centered outcomes and reduce healthcare costs?

Addressing these questions will require large pragmatic multicenter trials that evaluate not only glucose control but also mortality, functional recovery, healthcare utilization and cost-effectiveness.

CONCLUSION

Hyperglycemia remains one of the most common and clinically significant metabolic abnormalities in critically ill adults. Over the past 20 years, research has shown that both severe hyperglycemia and hypoglycemia can lead to adverse outcomes. This has shifted the focus from strict glucose control to a more moderate approach that prioritizes safety. Currently, evidence supports initiating intravenous insulin when blood glucose remains at or above 180 mg/dL, with a target range of 140 to 180 mg/dL. This should be achieved using standardized insulin infusion protocols and regular glucose monitoring.

Recognizing the prognostic importance of glycemic variability, time in range and the SHR has broadened the definition of dysglycemia beyond absolute glucose levels, promoting more personalized metabolic treatment. Meanwhile, advances in CGM, automated insulin dosing algorithms, hybrid closed-loop systems and AI are accelerating the shift toward precision glycemic control.

Future progress will depend on conducting rigorous clinical trials to ensure the safe adoption of these technologies in standard critical care. Personalized glucose goals, technology-aided insulin delivery and data-driven clinical decision support could enhance the safety and efficiency of inpatient glycemic control. As these innovations advance, they are likely to shift glucose management from a reactive process based on periodic measurements to a continuous, tailored and predictive system that improves outcomes for critically ill patients.

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