MANAGEMENT OF DIABETES AND HYPERGLYCEMIA IN HOSPITALIZED PATIENTS

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ABSTRACT

Diabetes is the most prevalent metabolic disorder, and in 2021, the International Diabetes Federation estimated that it affected 537 million adults globally. In 2024, the United States Centers for Disease Control reported that 38.1 million adult Americans, or 14.7% of the adult population, have diabetes. Patients with diabetes have a 3-4-fold greater chance of hospitalization compared to those without diabetes. In 2020, in the U.S., there were over 7.86 million hospital discharges for adults listed as having diabetes. Hyperglycemia, defined as a blood glucose greater than 140 mg/dl (7.8 mmol/l), is reported in 22-46% of non-critically ill hospitalized patients. Extensive data indicates that inpatient hyperglycemia, in patients with or without a prior diagnosis of diabetes, is associated with an increased risk of complications and mortality. In 2025, the American Diabetes Association (ADA) recommends that once therapy is initiated, a glycemic goal of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill (ICU) individuals with hyperglycemia. More stringent individualized glycemic goals may be appropriate for selected critically ill individuals if they are achieved without significant hypoglycemia. However, for non-critically ill (non-ICU) individuals, a glycemic goal of 100-180 mg/dL (5.6-10.0 mmol/L) is recommended, if achieved without significant hypoglycemia. Insulin remains the best way to control hyperglycemia in the inpatient setting, especially in critically ill patients. Intravenously administered insulin is the preferred method to achieve the recommended glycemic target in the ICU. In 2025, the ADA changed its recommendations on using SGLT2 inhibitors in inpatients. They now suggest that in people with type 2 diabetes and heart failure, SGLT2 inhibitors may be started or continued if there are no contraindications (which include prolonged fasting or post-operative recovery). The use of GLP-1 receptor agonists was not recommended in previous guidelines because of the need for more safety and efficacy studies in the inpatient setting. However, increasing evidence indicates that treatment with oral agents such as DPP4 inhibitors, alone or combined with basal insulin, is safe and effective in general medicine and surgery patients with mild to moderate hyperglycemia.

INTRODUCTION

Diabetes is the most prevalent metabolic disorder, affecting more than 537 million adults globally and is projected to rise to almost 800 million (10.9% of

the adult population) by 2045 (1). In the United States, data from the National Diabetes Statistics Report in 2023 estimated that 38.4 million people of all ages or 14.7% of all U.S. adults had diabetes (2). The percentage of the population with diagnosed diabetes is expected to rise, with one study projecting that as many as one in three U.S. adults will have diabetes during their lifetime (3). People with diabetes have a 35% greater chance of referral for elective operations and a 3-4-fold greater chance of hospitalization compared to those without diabetes (4-7). Data from the US and Scotland estimate that of those individuals with a discharge diagnosis of diabetes, 30% will require two or more hospitalizations in any given year (5; 6; 8). In 2020, in the U.S., there were over 7.86 million hospital discharges for adults listed as having diabetes, (i.e., diabetes as either a principal diagnosis for hospitalization or as a secondary diagnosis, coexisting condition) (9). Data from the USA suggest that the prevalence of diabetes in the adult inpatient population has increased by 2.5% annually from 17.1% to 27.3% between 2000 and 2018 (10). In the UK, the annual National Diabetes Inpatient Audit suggested that the prevalence of diabetes amongst inpatients had risen from 15% in 2010 to almost 20% in 2019 (11). In addition, those hospitalized with a diagnosis of diabetes stay in the hospital for longer than those without a diagnosis of diabetes admitted for the same condition (12; 13).

Diabetes was the 8th leading cause of death in the United States in 2021, accounting for 31.1 deaths per 100,000 of the population (2). A further 120.3 per 100,000 people had diabetes listed as a contributing factor towards the cause of death (2). Not only does diabetes have a significant economic impact on those living with the condition, but it also imposes a substantial burden on the economy, with a total estimated cost of treating people diagnosed with diabetes in the United States in 2022 of $413 billion – or 25% of all health care spending in the US (14). This included $306.6 billion in direct medical costs. It is estimated that a further cost of $96.5

billion is incurred due to reduced productivity (14). Data from Ireland estimated that the overall cost of treating diabetes represented between 12 and 14% of the annual health budget. The cost per admission for someone with type 1 or type 2 diabetes was €4,027 and €5,026, respectively (15). Globally, diabetes care costs have been estimated at $1.3 trillion, rising to an estimated $2.1-2.5 trillion by 2030 (16; 17). This represents a rise in spending on diabetes as a proportion of global gross domestic product from 1.8% in 2015 to 2.2% in 2030 (17). Other than the costs of diabetes medications, the most significant component of this medical expenditure is hospital inpatient care (13; 18).

Hyperglycemia is defined as a blood glucose concentration greater than 140 mg/dl (7.8 mmol/l) (19-21). It is not just found in those with a pre-existing diagnosis of diabetes but in those with stress hyperglycemia or previously undiagnosed diabetes. The prevalence has been reported to be 22% to 46% in non-critically ill hospitalized patients (8; 19). Extensive observational and trial data indicate that inpatient hyperglycemia, in patients with or without a prior diagnosis of diabetes, is associated with an increased risk of complications and mortality, a longer hospital stay, a higher admission rate to the intensive care unit (ICU), and a higher need for transitional or nursing home care after hospital discharge (8; 22; 23).

Several studies and meta-analyses have shown that attempting 'tight' glycemic control using intensive insulin therapy is associated with an increased risk of hypoglycemia (24-28), which has been associated with increased morbidity and mortality in hospitalized patients (19; 29-34). Thus, while insulin therapy is recommended for managing hyperglycemia in hospitalized patients, the concern about hypoglycemia has led leading professional organizations worldwide to recommend targets that avoid the risk of hypoglycemia (20; 27; 35-38).

This chapter reviews the pathophysiology of hyperglycemia during illness, the mechanisms for increased complications and mortality due to hyperglycemia and hypoglycemia, and the evidence supporting different therapies and approaches for the management of inpatient diabetes and hyperglycemia in critical care, general medicine, and surgical settings.

PREVALENCE OF DIABETES AND HYPERGLYCEMIA IN THE HOSPITALIZED PATIENT

Observational studies have reported a prevalence of hyperglycemia and diabetes ranging from 38% to 40% in hospitalized patients (8) and in 70-80% of those with diabetes who have a critical illness or cardiac surgery (39-41). A 2017 report using point-of-care bedside glucose tests data in almost 3.5 million people (653,359 ICU and 2,831,436 non-ICU) from 575 hospitals in the United States reported a prevalence of hyperglycemia (defined as a glucose level >180 mg/dl [10.0 mmol/l]) of 32.2% in ICU patients and in 32.0% of non-ICU patients (39). A study of 893 people across 69 ICUs in France reported a prevalence of hyperglycemia (>180 mg/dl [10 mmol/l]) of 45% (42). Other USA data suggest that between 2000 and 2018, the prevalence of diabetes amongst adult inpatients increased by 2.5% per year from 17.1% to 27.3% (10), and that over 33% of all hospital discharges in 2020 had diabetes listed as a diagnosis (9). However, this does not include those individuals who develop stress hyperglycemia. The American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) consensus on inpatient hyperglycemia defined stress hyperglycemia or hospital-related hyperglycemia as any blood glucose concentration >140 mg/dl (>7.8 mmol/l) in patients without a prior history of diabetes (19; 20). The data from the US

included those with newly identified diabetes or stress hyperglycemia as well as those with a prior diagnosis of diabetes (39). Although stress hyperglycemia typically resolves as the acute illness or surgical stress abates, a significant proportion (up to 60% in some reports) develop confirmed diabetes at 6-12 months after discharge (43; 44). A guide from the UK on the management of 'diabetes at the front door', also recommends that any individual without diabetes who presents acutely unwell should have a capillary glucose measurement and blood/urine ketone measurement taken, but that if it is high on admission (i.e. >140mg/dl [7.8 mmol/l]) and subsequently goes down to normal, then a diagnosis of stress hyperglycemia should be made and documented to the primary care team (21).

Measurement of HbA_{1c} is indicated in people with hyperglycemia without a history of diabetes to differentiate between stress-induced hyperglycemia and previously undiagnosed diabetes (21; 45-48). The ADA also recommends that an HbA_{1c} be done in those with diabetes who have not had it measured in the preceding 3 months (48). The Endocrine Society and the UK Joint British Diabetes Societies for Inpatient Care (JBDS) recommendations indicate that people hospitalized with elevated blood glucose >140 mg/dl (7.8 mmol/l) and an HbA_{1c} of 6.5% (48 mmol/mol) or higher can be identified as having diabetes (19; 21). Given the increasing prevalence of diabetes, the UK has also produced a calculator to help teams work out their optimal staffing levels (49).

PATHOPHYSIOLOGY OF HYPERGLYCEMIA DURING ILLNESS

In subjects without diabetes during the fasted state, plasma glucose is maintained between 70 – 100 mg/dl (3.9 – 5.6 mmol/l) by a finely regulated balance between glucose production from the liver

and kidneys and glucose utilization in peripheral tissues. Maintenance of near-normal glucose concentration is essential for cardiovascular and central nervous system function because the brain can neither synthesize nor store glucose (50; 51).

Systemic glucose balance is maintained by dynamic, minute-to-minute regulation of endogenous glucose production and glucose utilization by peripheral tissues (52). Glucose production is accomplished by gluconeogenesis or glycogenolysis primarily in the liver and, to a lesser degree, by the kidneys (53; 54). Gluconeogenesis results from converting non-carbohydrate precursors such as lactate, alanine, and glycerol to glucose in the liver (55). Excess glucose is polymerized into glycogen, mainly stored in the liver and muscle. Hyperglycemia develops because of three processes: 1) increased gluconeogenesis, 2) accelerated glycogenolysis, and 3) impaired glucose utilization by peripheral tissues (Figure 1).

Absolute or Relative Insulin Deficiency and Increased Counterregulatory Hormones

Adipose Tissue
TG
↑ Lipolysis
Free Fatty Acids
Glycerol
Liver
Amino acids
Lactate
↑ Protein breakdown
Muscle
↑Glucose output
↑Glycogenolysis
↓ Glucose utilization

IV dextrose
Glucocorticoids
Catecholamines
Inflammatory cytokines
Parenteral nutrition
Enteral nutrition

Hyperglycemia

Circulatory & electrolytes effects
Volume depletion
Hypoperfusion
Electrolyte loss
Acid base disturbances

Tissue effects
Reduced nitric oxide
Superoxide generation
Endothelial dysfunction
Platelet activation
Immune dysregulation
Mitochondrial injury
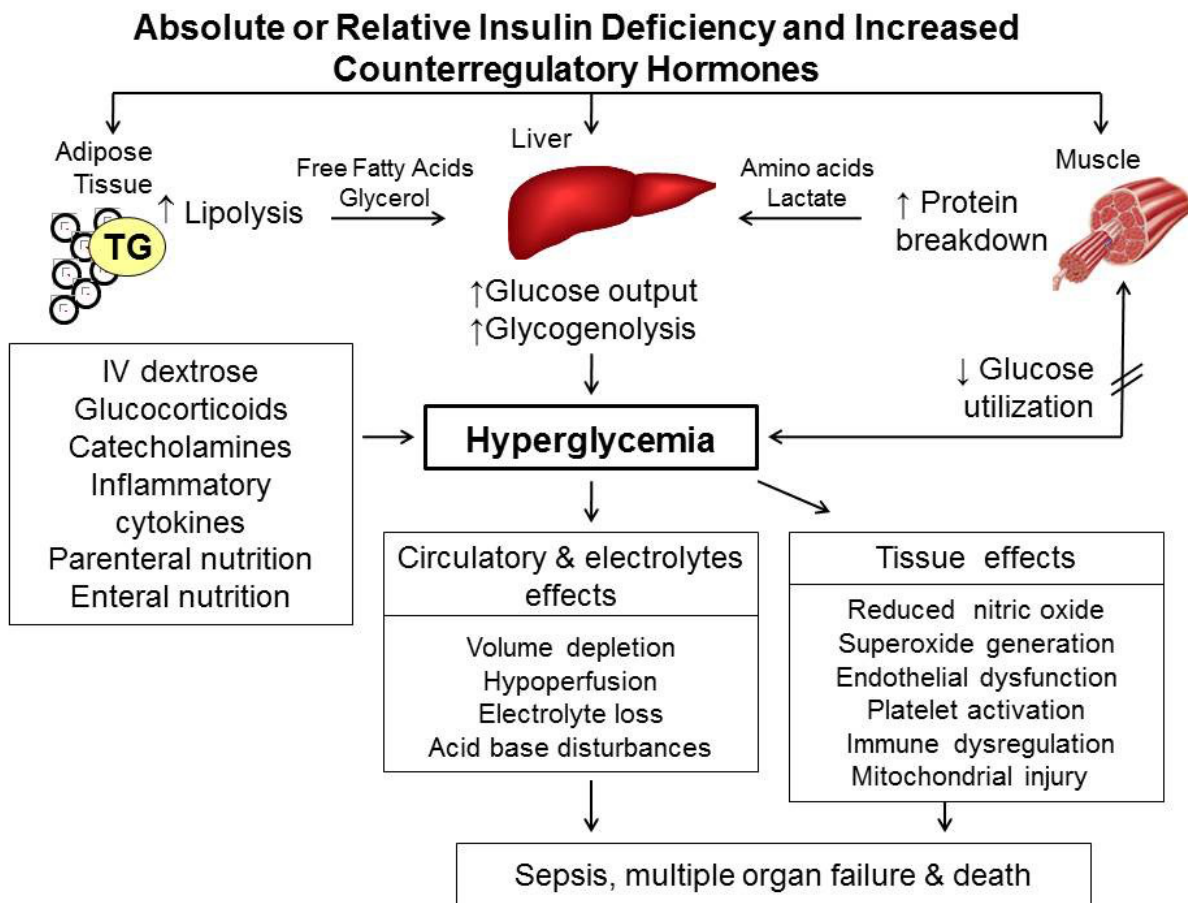
Sepsis, multiple organ failure & death

Figure 1. Pathogenesis of hyperglycemia. Hyperglycemia results from increased hepatic glucose production and impaired glucose utilization in peripheral tissues. Reduced insulin and excess counter-regulatory hormones (glucagon, cortisol, catecholamines, and growth hormone) increase lipolysis and protein breakdown (proteolysis) and impair glucose uptake by peripheral tissues. Hyperglycemia causes osmotic diuresis, leading to volume depletion, decreasing glomerular filtration rate, and worsening hyperglycemia. At the cellular level, increased blood glucose concentrations result in mitochondrial injury by generating reactive oxygen species and endothelial dysfunction by inhibiting nitric oxide production. Hyperglycemia increases levels of pro-

inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin [IL]-6, leading to immune system dysfunction. These changes can eventually lead to an increased risk of infection, impaired wound healing, multiple organ failure, prolonged hospital stay, and death. Adapted from ref (25).

From the quantitative standpoint, inappropriately increased hepatic glucose production represents the major pathogenic disturbance. Increased hepatic glucose production results from the high availability of gluconeogenic precursors. These include the amino acids alanine and glutamine, which result from accelerated proteolysis and decreased protein synthesis; lactate, which results from increased muscle glycogenolysis; glycerol, which results from increased lipolysis; and the increased activity of gluconeogenic enzymes (phosphoenol pyruvate carboxykinase, fructose-1,6-bisphosphatase, and pyruvate carboxylase) (53; 55).

Glucose metabolism is maintained by an interaction of glucoregulatory hormones – insulin and counter-regulatory hormones (glucagon, cortisol, epinephrine, norepinephrine, and growth hormone). Insulin controls hepatic glucose production by suppressing hepatic gluconeogenesis and glycogenolysis. Depending on the concentration in the circulation, insulin inhibits glycogenolysis and protein breakdown and, at higher concentrations, promotes protein anabolism in insulin-sensitive tissues such as muscle, glucose uptake, and glycogen synthesis (52; 56; 57). In addition, insulin is a potent inhibitor of lipolysis, free fatty acid oxidation, and ketogenesis (56-58).

Counter-regulatory hormones also play an essential role in regulating glucose production and utilization. Glucagon is the most important glycogenolytic hormone, and therefore regulates hepatic glucose production in healthy individuals and in every state of hyperglycemia (53). During stress, excess concentration of counter-regulatory hormones results in altered carbohydrate metabolism by inducing insulin resistance, increasing hepatic glucose production, and reducing peripheral glucose utilization. In addition, high epinephrine levels stimulate glucagon secretion and inhibit insulin release by pancreatic β-cells (59; 60).

The development of hyperglycemia results in an inflammatory state characterized by an elevation of pro-inflammatory cytokines and increased oxidative stress markers (61-63). Circulating levels of TNF-α, IL-6, IL1-ß, IL-8, and C-reactive protein are significantly increased two- to fourfold on admission in people with severe hyperglycemia compared with control subjects, and levels returned to normal levels after insulin treatment and resolution of hyperglycemic crises (61). Raised concentrations of TNF-α lead to insulin resistance at the level of the insulin receptor and through altered regulation of the insulin-signaling pathway (62; 64). In addition, preventing insulin-mediated activation of phosphatidylinositol 3- kinase TNF-α reduces insulin-stimulated glucose uptake in peripheral tissues (62; 64; 65).

CONSEQUENCES OF HYPERGLYCEMIA IN THE HOSPITALIZED PATIENTS

A large body of literature, including observational and prospective randomized clinical trials, in people with and without diabetes, as well as those who are critically or non-critically ill has shown a strong association between hyperglycemia (in particular, a blood glucose >200mg/dl [11.0mmol/l]) and poor clinical outcomes, such as mortality, infections, and hospital complications compared to those with a

glucose concentration of <100mg/dl (5.6mmol/l) (5; 66-76). This association correlates with the severity of hyperglycemia prior to or on admission and during the hospital stay (72; 77-79). Of interest, increasing evidence indicates an increased risk of complications and mortality in patients without a history of diabetes (stress-induced) compared to patients with a known diagnosis of diabetes (8; 69; 75; 77; 80; 81). It is not clear if stress hyperglycemia is the direct cause of poor outcomes or if it is a general marker of the severity of illness. However, there are data to show that those without a prior history of diabetes have fewer point-of-care glucose concentrations measured compared to those with diabetes, even when glucose concentrations are just as high (75; 82). In those who had diabetes, having more point-of-care tests increases contact with the ward staff, suggesting that impending complications may be picked up sooner, resulting in lower mortality. These data correlate with other work that also shows that those with lower preoperative HbA$_{1c}$ lower the number of post-operative glucose checks in a general surgical population (83).

The mechanisms implicated in the detrimental effects of hyperglycemia during acute illnesses are not entirely understood. Current evidence indicates that severe hyperglycemia results in impaired neutrophil granulocyte function, high circulating free fatty acids, and overproduction of pro-inflammatory cytokines and reactive oxygen species (ROS) that can result in direct cellular damage and endothelial and immune dysfunction (84; 85).

The majority of evidence linking hyperglycemia and poor outcomes comes from studies in the ICU. Falciglia et al., in a retrospective study of over 250,000 veterans admitted to various ICUs, reported that hyperglycemia is an independent risk factor for mortality and complications (77). In a nonrandomized, prospective study, Furnary et al. followed 3,554 people with diabetes who underwent

coronary artery bypass graft. These were treated with either intermittent subcutaneous insulin (SCI) or with a continuous intravenous insulin infusion (CIII). The group treated with SCI achieved an average blood glucose of 214 mg/dl (11.9 mmol/l), compared to 177 mg/dl (9.8 mmol/l) in the CIII group. The CIII group had significantly fewer deep sternal wound infections and a 50% lower risk-adjusted mortality (73; 86). In other ICU studies, patients with blood glucose levels >200 mg/dl (>11.1 mmol/l) were shown to have higher mortality compared to those with blood glucose levels <200 mg/dl (<11.1 mmol/) (72; 75). Importantly however, once again it has been shown that it was those people who were not previously known to have diabetes yet who developed hyperglycemia on the ICU who fared worse (75; 87). This was confirmed by another ICU study looking at almost 350,000 people, looking at the outcomes of those with sepsis (88). These authors showed that having hyperglycemia without a prior diagnosis of diabetes was associated with an increased stay in hospital and ICU and greater 90-day mortality (88). However, there was no difference in outcomes for those with diabetes unless they had experienced severe hypoglycemia (<40 mg/dl [2.2 mmol/l]), in which case mortality rose (OR 2.95 95%CI 1.19-7.32) (88). Another ICU study randomized 9230 people who were not given early parenteral nutrition to liberal glucose control (insulin only started if glucose rose to >215 mg/dl [>11.9 mmol/l]), or tight glucose control with glucose concentrations maintained between 80 and 110 mg/dl (4.4 – 6.1 mmol/l). These authors showed no differences in outcome, including length of time in ICU, infection rates, time on respiratory or hemodynamic support, or mortality. The only differences were lower severe acute kidney injury incidence and cholestatic liver dysfunction in the tight glycemic control arm (89).

The association of hyperglycemia and poor outcomes also applies to those not in ICU but admitted to general medicine, surgery, or mental health services. In such individuals, hyperglycemia

is associated with poor hospital outcomes, including prolonged hospital stay, infections, disability after hospital discharge, and death (5; 8; 66; 67; 81; 90). In a study of 1,886 patients admitted to a community hospital, mortality in the general floors was significantly higher in patients with newly diagnosed hyperglycemia and with known diabetes compared to subjects with normal glucose values (10% vs. 1.7% vs. 0.8%, respectively, p < 0.01) (8). In a prospective cohort multicenter study of 2,471 patients with community-acquired pneumonia, those with an admission glucose level of >198 mg/dl (>11.0 mmol/l) had a greater risk of mortality and complications than those with glucose <198 mg/dl (<11.0 mmol/l) (91). The risk of complications increased by 3% for each 18 mg/dl (1.0 mmol/l) increase in admission glucose (91). In a retrospective study of 348 patients with chronic obstructive pulmonary disease and respiratory tract infection, the relative risk of death was 2.1 in those with a blood glucose of 126-160 mg/dl (7.0-8.9 mmol/l), and 3.4 for those with a blood glucose of >162 mg/dl (9.0 mmol/l) compared to patients with a blood glucose of 108 mg/dl (6.0 mmol/l) (92). Similar data from a systematic review and meta-analysis from 38 studies of people who needed hospitalization for community-acquired pneumonia showed that in those without a prior diagnosis of diabetes, hyperglycemia was associated with an almost doubling of the need for ICU admission (crude OR 1.82, 95% CI 1.17 to 2.84) and in-hospital mortality (adjusted OR 1.28, 95% CI 1.09 to 1.50) (81). Those people already known to have diabetes had no increased risk of either.

General surgery patients with hyperglycemia during the perioperative period are also at increased risk for adverse outcomes. Reviews of diabetes and the risk of surgical site infection across a variety of surgical specialties have shown that high peri-operative glucose is associated with an increased risk of infection (93; 94). In a case-control study, elevated preoperative glucose levels increased the risk of postoperative mortality in patients undergoing elective non-cardiac non-vascular surgery (95). Patients with glucose levels of 110-200 mg/dl (5.6-11.1 mmol/l) and those with glucose levels of >200 mg/dl (>11.1 mmol/l) had, respectively, 1.7-fold and 2.1-fold increased mortality compared to those with glucose levels <5.6 mmol/l (<110 mg/dl) (95). In another study, patients with glucose levels >220 mg/dl (>12.2 mmol/l) on the first postoperative day had a rate of infection 2.7 times higher than those who had serum glucose levels <220 mg/dl (<12.2 mmol/l) (96). Other authors showed an increase of postoperative infection rate by 30% for every 40mg/dl (2.2 mmol/l) rise in postoperative glucose level above 110 mg/dl (6.1 mmol/l) (96). Further, a study looking at perioperative glycemic control and the effect on surgical site infections in people with diabetes undergoing foot and ankle surgery showed that 11.9% of those with a serum glucose ≥200 mg/dl (11.1 mmol/l) during the admission developed a surgical site infection versus only 5.2% of those with a serum glucose <200 mg/dl (11.1 mmol/l) (odds ratio = 2.45; 95% CI 1.09-5.52, P = 0.03) (97). Lastly, a prospective randomized study looking at the impact of glycemic control at 1-year post liver transplant showed that in those randomized to glycemic control of blood glucose below 140 mg/dl (7.8 mmol/l), any infection within one year occurred in 35 of the 82 patients (42.7%) versus 54 of 82 (65.9%) in those randomized to glycemic control of 180 mg/dl (10.0 mmol/l) (P = 0.0046) (98).

Emerging evidence suggests that early intervention and the use of technology allowing proactive identification of people at risk help to reduce hospital-acquired infection rates, episodes of hyper- and hypoglycemia, and, in some cases, length of stay (99-102). A meta-analysis also shows that improving peri-operative glycemic control reduced postoperative infection rates (103).

In summary, despite a large amount of work having been done, and the numerous data showing the

association – but not causation – between hyperglycemia and poor outcomes, and because there remain a very few robust intervention studies showing a benefit of glycemic control, the optimal blood glucose concentration for people on ICU has yet to be determined (104; 105).

GLYCEMIC TARGETS IN THE ICU AND NON-ICU SETTINGS

The American Diabetes Association (ADA) and American Association of Clinical Endocrinology (AACE) task force on inpatient glycemic control and other groups recommended differing glycemic targets in the ICU setting (20) (Table 1). These guidelines suggest targeting a BG level between 140 and 180 mg/dl (7.8 and 10.0 mmol/l) for the majority of ICU patients and a lower glucose target between 110 and 140 mg/dl (6.1 and 7.8 mmol/l) in selected ICU patients (i.e., centers with extensive experience and appropriate nursing support, cardiac surgical patients, patients with stable glycemic control without hypoglycemia). Glucose targets >180 mg/dl (>10.0 mmol/l) or <110 mg/dl

(<6.1 mmol/l) are not recommended in ICU patients. There is an argument that lowering glucose thresholds for hospital patients will likely be associated with harm (32). Still, an equally persuasive argument suggests that implementing the thresholds advocated by national and organizational guidelines has led to safer care (106).

The Society of Critical Care Medicine (SCCM) guidelines for the management of hyperglycemia in critically ill (ICU) patients recently "recommended against" titrating an insulin infusion to a lower glucose target of 80–139 mg/dL (4.4–7.7 mmol/L) as compared with a higher BG target range of 140–200 mg/dL (7.8–11.1 mmol/L) to reduce the risk of hypoglycemia (107). They also recommended that clinicians should initiate glycemic management protocols and procedures to treat persistent hyperglycemia greater than or equal to 180 mg/dL (10 mmol/L) to maintain target glucose below <180 mg/dl (<10.0 mmol/l) in critically ill adults (107). They also suggest that the insulin regimen and monitoring system be designed to avoid and detect hypoglycemia (blood glucose <70 mg/dl [<3.9 mmol/l]) and to minimize glycemic variability.

Table 1. Major Guidelines for Treatment of Hyperglycemia in a Hospital Setting		
	ICU	Non-ICU
ADA/AACE (20; 108)	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]. More stringent goals (110 – 140 mg/dl [6.1 – 7.8 mmol/l]) or 100 – 180 mg/dL (5.6 –10.0 mmol/L), may be appropriate for selected patients and are acceptable if they can be	No specific guidelines. Insulin therapy should be initiated for the treatment of persistent hyperglycemia ≥180 mg/dL (10.0 mmol/L) and targeted to a glucose range of 140 –180 mg/dL (7.8 – 10.0 mmol/L) for most critically ill patients. More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected

	achieved without significant hypoglycemia	patients (e.g., critically ill postsurgical patients or patients with cardiac surgery) as long as they can be achieved without significant hypoglycemia. Less stringent targets (e.g., >250 mg/dL (13.9 mmol/L) may be appropriate in people with severe comorbidities or end of life care.
ACP (27)	Recommends against intensive insulin therapy in those with or without diabetes in surgical / medical ICUs Treatment goal: target glucose between 140 – 200 mg/dl (7.8 – 11.0 mmol/l), in people with or without diabetes, in surgical / medical ICUs	
Critical Care Society (107)	BG >180 mg/dl (>10.0 mmol/l) should trigger insulin therapy. Treatment goal: maintain glucose <180 mg/dl (<10.0 mmol/l) for most adults in ICU. Maintain glucose levels <180 mg/dl (10.0 mmol/l) while avoiding hypoglycemia.	
Endocrine Society (19; 109)		Pre-meal glucose target <140 mg/dl (<7.8mmol/l) and random blood glucose <180 mg/dl (<10.0 mmol/l). Those with insulin treated diabetes aim for a target glucose of 100 – 180 mg/dL (5.6 – 10 mmol/L). A lower target range may be appropriate in people able

		to achieve and maintain glycemic control without hypoglycemia. A glucose of <180 – 200 mg/dl (<10.0 – 11.0 mmol/l) is appropriate in those with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia. Adjust antidiabetic therapy when glucose falls <100 mg/dl (<5.6 mmol/l) to avoid hypoglycemia.
Society of Thoracic Surgeons (110)	Continuous insulin infusion preferred over SC or intermittent intravenous boluses. Treatment goal: Recommend glucose <180 mg/dl (<10.0 mmol/l) during surgery (≤110 mg/dl [≤6.1 mmol/l] in fasting and pre-meal states)	
Joint British Diabetes Society for Inpatient Care (111)		Target blood glucose levels in most people of between 108 – 180 mg/dl (6.0 – 10 mmol/l) with an acceptable range of between 72 – 216 mg/dl (4.0 – 12.0 mmol/l).

AACE/ADA, American Association of Endocrinologists and American Diabetes Association joint guidelines; ACP, American College of Physicians; ADA, American Diabetes Association; ICU, intensive care unit; SC, subcutaneous.

In the non-ICU setting, the Endocrine Society and the ADA/AACE Practice Guidelines recommended a pre-meal glucose of <140 mg/dl (<7.8 mmol/l) and a random BG of <180 mg/dl (<10.0 mmol/l) for the majority of non-critically ill patients treated with insulin (19; 20; 35; 109). More recently, the American Diabetes Association has recommended that target glucose for most general medicine and surgery patients in non-ICU settings should be between 140 – 180 mg/dl (7.8 – 10.0 mmol/l) (108). In contrast, higher glucose ranges (>200 mg/dl [>11.1 mmol/l]) may be acceptable in people who are terminally ill or in those with severe comorbidities as a way of avoiding symptomatic hyperglycemia (19; 112).

Guidelines from the JBDS in the UK published over the last few years aim for target blood glucose concentrations in most people between 108 – 180 mg/dl (6.0 – 10.0 mmol/l) with an acceptable range of between 72 – 216 mg/dl (4.0 – 12.0 mmol/l) (111).

Table 1 summarizes the currently available guidelines for managing hyperglycemia in the hospital setting.

EVIDENCE FOR CONTROLLING HYPERGLYCEMIA IN ICU AND NON – ICU SETTINGS

In 2001, the Leuven surgical ICU study promoted intensive glycemic control in the critical care setting (113). This study randomized 1,548 people admitted to the surgical ICU (63% cardiac cases, 13% with diabetes, with most receiving early parenteral nutrition). Individuals were randomized to either conventional therapy, with target glucose between 180 – 200 mg/dl (10.0 – 11.1 mmol/l), or intensive treatment to target glucose between 80 – 110 mg/dl (4.4 – 6.1 mmol/l). Those in the conventional arm had a mean daily glucose average of 153 mg/dl (8.5 mmol/l), and those in the intensive arm had an average glucose of 103 mg/dl (5.7 mmol/l). Those in the intensive group had significantly less bacteremia, fewer antibiotic requirements, lower length of ventilator dependency, lower number of ICU days, and an overall 34% reduction in mortality (113). Following a similar study design, the same group of investigators randomized people to a medical ICU (18% with diabetes) and reported that intensive insulin therapy (mean daily glucose of 111 mg/dl [6.2 mmol/l]) resulted in less ICU and total hospital complications in those with three days of insulin treatment (114). These two studies together, based on the positive outcomes on morbidity and mortality, suggested a glycemic target in the ICU of 140 – 180 mg/dl (7.8 – 10.0 mmol/l) (20). There was also a realization that while lower targets may be appropriate for selected individuals, a target of <110 mg/dl (<6.1 mmol/l) was not recommended (20).

Many well-designed randomized controlled trials and meta-analyses have shown that such low glucose targets are difficult to achieve, even in environments with high staff-to-patient ratios, without increasing the risk for severe hypoglycemia (24; 115-117). In addition, these and other studies failed to show improvement in clinical outcomes and have even shown increased mortality risk with intensive glycemic control, targeting glucose concentrations of (80 – 110 mg/dl [4.4 – 6.1 mmol/l]) versus conventional glycemic control (140 – 200 mg/dl [7.8 – 11.0 mmol/l]) (Table 2) (29; 115-118). Most of these studies showed no differences in clinical outcomes between groups but had an increased risk of severe hypoglycemia in the intensively treated arms. One study in ICU patients was the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial, which randomized over 6104 subjects to receive either conventional glycemic control to target glucose <180 mg/dl [<10.0 mmol/l]) or intensive glycemic control (target 81 – 108 mg/dl [4.5 – 6.0 mmol/l]). This study also reported no difference in hospital mortality but found increased mortality at 90 days of follow-up (24.9% vs. 27.5%, p=0.02) (24). In a subsequent analysis of the trial, the NICE-SUGAR investigators reported a higher frequency of hypoglycemia in the intensive arm (6.8% vs. 0.5%), and those with hypoglycemia had a ~2-fold increase in mortality compared to patients without hypoglycemia (29). More recently, Gunst et al. recently published the results of a multicenter, randomized trial involving 9230 patients in medical and surgical ICUs (89). 4622 patients were assigned to liberal glucose control, where insulin was initiated only when the blood glucose level was above 215 mg per deciliter (11.9 mmol per liter), and 4608 patients were assigned to tight glucose control, targeting a glucose level between 80 and 110 mg per deciliter. The primary outcome, the duration of time in ICU care, did not differ significantly between the two trial groups. The hazard ratio for earlier discharge alive with tight glucose control was 1.00 with a 95% confidence interval of 0.96 to 1.04. Effective glycemic separation between the groups was observed, with a median absolute difference of -28 mg/dl (-1.6 mmol/l) in daily

blood glucose levels. Additionally, the safety outcome, mortality within 90 days after randomization, was 10.1% in the liberal-control group and 10.5% in the tight-control group. The incidence of other secondary outcomes, including severe hypoglycemia, time to discharge alive from the hospital, use of respiratory support, or in-hospital mortality, were no different between intensive and relaxed glycemic targets, except for a trend in lower rates of liver and kidney injury in the tight control group. Umpierrez recently summarized the data on mortality and outcomes of ICU RCTs (119).

Increasing evidence indicates that high pre-admission glycemic control – as measured by HbA_{1c} >8.0% (64mmol/mol) is associated with lower mortality than those with an HbA_{1c} <6.5% (48mmol/mol) (120). Whether this is due to an increased risk of hypoglycemia in the low HbA_{1c} group or an increased frequency of monitoring or bedside vigilance in those with higher glucose or preadmission HbA_{1c} remains unknown (75; 83).

Table 2. Clinical Trials of Intensive Glycemic Control in ICU Populations				
Study	**Setting**	**Population**	**Percentage with diabetes**	**Clinical Outcome**
Malmberg, 1994 (121)	CCU	People with diabetes with suspected or confirmed acute MI	100	28% decrease mortality after 1 year
Furnary, 1999 (73)	CCU	People with diabetes undergoing CABG	100	65% decrease in deep sternal wound infection rate
Van den Berghe, 2001 (113)	Surgical ICU	Mixed, with CABG	13	34% decrease in mortality
Furnary, 2003 (86)	CCU	People with diabetes undergoing CABG	100	50% decrease in adjusted mortality rate
Krinsley, 2003 (72)	Medical and surgical ICU	Mixed	22.4	27% decrease in mortality
Lazar, 2004 (122)	Operating room and ICU	People with diabetes undergoing CABG	100	60% decrease of post - operative atrial fibrillation
Van den Berghe, 2006 (114)	Medical ICU	Mixed	17	18% decrease mortality
Gandhi, 2007 (123)	Operating Room	Mixed, undergoing cardiac surgery	19.6	No difference in mortality; increase in stroke rate in the intensive treatment arm

VISEP, 2008 (115)	Medical ICU	Mixed, admitted with sepsis	30	No differences in 28-day or 90-day mortality, end-organ failure, length of stay
De La Rosa, 2008 (116)	Medical and surgical ICU	Mixed	12	No differences in 28-day mortality or infection rate
Glucontrol, 2009 (124)	Medical and surgical ICU	Mixed	18	No difference in 28-day mortality
NICE-SUGAR, 2009/2012 (24; 29)	Medical and surgical ICU	Mixed	20	No difference in 90-day mortality
Boston Children's (SPECS), 2012 (125; 126)	Cardiac ICU	Cardiac surgery, people without diabetes	0	No differences in 30-day mortality, length of stay, in the cardiac ICU, length of hospital, duration of mechanical ventilation and vasoactive support, or measures of organ failure
ChiP, 2014 (127)	Pediatric ICU	Critical illness/injury/major surgery, those without diabetes.	0	No difference in 30-day mortality. Increased hypoglycemia in the intensive treated group
CGAO–REA, 2014 (128; 129)	Medical ICU	Mixed	23	No difference in 90-day mortality. Increased hypoglycemia in the intensive treated group
Okabayashi, 2014 (130)	Surgical ICU	Mixed	25.3	Decreased surgical site infection in the intensive treated group
Umpierrez (GLUCOCABG)	Surgical ICU	CABG	50%	No difference in mortality

2015				
Gunst et al ICU	ICU		XX	No difference in mortality

MI, myocardial infarction, ICU – Intensive Care Unit, CABG – Coronary artery bypass graft. Mixed-study enrolled those with and without diabetes.

The GLUCO-CABG trial was a randomized open-label clinical study that included those with and without diabetes undergoing CABG who experienced perioperative hyperglycemia, defined as a BG >140 mg/dl (>7.8 mmol/l) 6069 (70). A total of 302 people between 18 and 80 years of age were randomized to the intensive glycemic control group (target BG 100 – 140 mg/dl [5.6 – 7.8 mmol/l]) or the control group (BG 141 – 180 mg/dl [7.9 – 10.0 mmol/l]) in the ICU. After transitioning from the ICU to the telemetry floor, patients were managed with a single treatment protocol to maintain a glucose target of <140 mg/dl (<7.8 mmol/l) before meals during the hospital stay. The primary outcome included differences between intensive and conservative glucose control on a composite of perioperative complications, including sternal wound infection, bacteremia, respiratory failure, pneumonia, acute kidney injury, major adverse cardiovascular events including acute coronary syndrome, stroke, heart failure, and cardiac arrhythmias (70). The mean BG during the ICU stay was 132±14 mg/dl (7.3±0.8 mmol/l) in the intensive and 152±17 mg/dl (8.4±1.0 mmol/l) in the conservative group. Intensive glucose treatment resulted in a 20% reduction in perioperative complications compared to the conservative group (42% vs. 52%). Of interest, there were no differences in the rate of complications among patients with diabetes treated with intensive or conservative regimens (42% vs. 52%, p=0.08); however, intensive treatment was associated with a significantly lower rate of complications compared to the conservative group in those without diabetes (34% vs. 55%, p=0.008) (70). Hospitalization costs were lower in the intensive group (median [IQR]

$36,681 [28,488 – 46,074] vs. $40,913 [31,464 – 56,629], p=0.04), with an average total cost savings of $3,654 per case compared to conservative glucose control (131).

To date, few large studies have been conducted to determine if improved control in those not in ICU may result in reduced morbidity and mortality in general medical and surgical patients – indeed, until recently, for most people in hospital with diabetes while there are observational data to show that dysglycemia is harmful, there were little data to show that improving glycemic control helps (132). A randomized controlled trial from 2011 reported that improved glucose control using a basal-bolus regimen may reduce hospital complications in general surgery patients (71). Improving glucose control with a basal-bolus regimen significantly reduced the frequency of composite complications, including postoperative wound infection, pneumonia, bacteremia, and acute renal and respiratory failure (71). In that study, treatment with basal-bolus insulin reduced average total inpatient costs per day by 14% or $751 compared to treatment with a correction bolus dose insulin alone (133). Another study from Australia has shown that in a randomized study of 1371 surgical inpatients, 680 with even a single glucose value >200 mg/dl (11.1 mmol/l) received early intervention from the diabetes inpatient team (134). This led to reductions in glucose of a modest -5.4 mg/dl (-0.3 mmol/l), which still equated to a 4.6%, statistically significant reduction in hospital-acquired infections compared to those receiving standard care (134).

HYPOGLYCEMIA

Hypoglycemia is the most common side effect of treatment of all types of diabetes and stress hyperglycemia in the hospital setting. It presents a significant barrier to satisfactory long-term glycemic control. Hypoglycemia results from an imbalance between glucose supply, glucose utilization, and current insulin levels. Hypoglycemia is defined as a lower-than-normal level of blood glucose. Hypoglycemia is defined as any glucose level <70 mg/dl (<3.9 mmol/l) (108; 135) for hospital inpatients. Level 1 hypoglycemia is a glucose concentration of 54 – 70 mg/dL (3.0 – 3.9 mmol/L). Level 2 hypoglycemia is a blood glucose concentration of <54 mg/dL (3.0 mmol/L) (108). Severe hypoglycemia has been defined by many as <40 mg/dl (<2.2 mmol/l) (136), but a newer definition, Level 3 hypoglycemia, is a glucose concentration low enough where the individual requires third-party assistance to aid recovery (108). The UK JBDS guideline suggests that the lower limit of glucose in the inpatient population should be 108 mg/dl (6.0 mmol/l), and that the range between 72 – 108 mg/dl (4.0 – 6.0 mmol/l) be designated 'looming' hypoglycemia, to alert ward staff to take action because of the possibility that lower glucose levels may be associated with harm (137). The exception to this is those people on a diet only or those people on an insulin pump / closed loop system who can self-manage their diabetes while in the hospital.

The incidence of severe hypoglycemia in the different trials ranged between 5% and 28%, depending on the intensity of glycemic control in the ICU (138). Rates from subcutaneous insulin trials in non-critically ill patients range from less than 1% to 33% (71; 139; 140). In 2017, the UK National Diabetes Inpatient Audit (NaDIA) data showed that 18% of people with diabetes in hospital experienced one or more hypoglycemic episodes with a blood glucose <72mg/dl (<4.0 mmol/l) – down from 26%

in 2011, with 7% (1 in 14) of all inpatients experiencing episodes requiring third party assistance to administer rescue therapy (141). The NaDIA data also showed that those with type 1 diabetes had the highest prevalence, with 25% experiencing a severe hypoglycemic episode (141). Furthermore, 1.3% (1 in 80) of those in hospitals with diabetes required some form of injectable rescue treatment (i.e., IV glucose or IM glucagon), down from 2.1% in 2011 (141). The same data showed that the highest proportion of episodes occurred overnight (28%) between 05:00 and 09.00 AM when snack availability was likely the lowest (140; 141).

Table 3 lists some key factors that predict the likelihood of someone experiencing a hypoglycemic event while hospitalized. These also include older age, greater illness severity, diabetes, and the use of oral glucose-lowering medications and/or insulin (137; 142-145). In-hospital processes of care that contribute to the risk for hypoglycemia include unexpected changes in nutritional intake that are not accompanied by associated changes in the glycemic management regimen. Examples include (but are not limited to) cessation of nutrition for procedures, an adjustment in the amount of nutritional support, interruption of the established routine for glucose monitoring, deviations from the established glucose control protocols, and failure to adjust therapy when glucose is trending down, or steroid therapy is being tapered (137; 146; 147). A common cause of inpatient hypoglycemia is when handwritten insulin prescriptions lead to errors, including misreading, e.g., when 'U' is used for units (i.e., 4U becoming 40 units) or confusing the insulin name with the dose (e.g., Humalog Mix25 becoming Humalog 25 units) (148). Electronic prescribing has been associated with a lower rate of prescription errors (141).

However, other factors may also be involved, such as concurrent use of drugs with hypoglycemic

agents, e.g., warfarin, quinine, salicylates, fibrates, sulphonamides (including co-trimoxazole), monoamine oxidase inhibitors, NSAIDs, probenecid, somatostatin analogs, or selective serotonin reuptake inhibitors. Secondary causes of inpatient hypoglycemia include loss of counter-regulatory hormone function, e.g., Addison's disease, growth hormone deficiency, hypothyroidism, or hypopituitarism.

Table 3. Common Risk Factors for Developing Hypoglycemia in the Hospital
Prior episode of hypoglycemia
Older age
Chronic kidney disease
Congestive heart failure
Liver Failure
Sepsis
Malnutrition
Erratic eating patterns / Nutritional interruptions / Lack of access to carbohydrates
Malignancies
Insulin regimen
Type 1 diabetes
Mental status changes
Certain concomitants use of medications
Duration of diabetes

The development of hypoglycemia is associated with adverse hospital outcomes (29; 30; 117; 118; 124; 144; 149-155). Turchin et al. examined data from 4,368 admission episodes for people with diabetes, of which one-third were on regular insulin therapy (30). Patients experiencing inpatient hypoglycemia experienced a 66% increased risk of death within one year and spent 2.8 days longer in the hospital compared to those not experiencing hypoglycemia. A 2019 systematic review and meta-analysis of hospital-acquired hypoglycemia in non-ICU patients suggested that adults exposed to glucose levels <72 mg/dl (<4.0 mmol/l) experienced a mean increased length of hospital stay of 4.1 days (95% CI 2.36 – 5.79) compared to those who did not experience hypoglycemia (144). The same dataset suggested an increased relative risk of in-hospital mortality for non-ICU patients of 2.09 (95% CI 1.64 – 2.67) (144). There was a non-significant reduction in mortality for those in ICU of 0.75 (95% CI 0.49 – 1.16)

(144). The odds ratio (95% confidence interval) for mortality associated with one or more episodes was 2.28 (1.41-3.70, p=0.0008) among a cohort of 5,365 patients admitted to a mixed medical-surgical ICU (142). In a larger cohort of over 6,000 patients, hypoglycemia was associated with longer ICU stays and greater hospital mortality, especially for patients with more than one episode of hypoglycemia (29). These data strengthen the argument to have potentially less strict glycemic targets for those not on ICU (32; 137). For example, if an individual has a glucose of 75 mg/dl (4.2 mmol/l), and is on an intravenous insulin infusion, by the time their bedside capillary glucose is next measured, they may have a glucose well below 72 mg/dl (4.0 mmol/l), thus they have come to potential harm. Indeed, data published from previous NaDIA surveys and NaDIA Harms using data from over 100 hospitals across the UK showed several serious adverse events, including seizures, permanent cerebral damage, cardiac

arrests, and deaths. Insulin therapy was implicated in several of these events (33; 34; 156; 157). The counterargument is that there are initiatives to reduce the risk of developing inpatient hypoglycemia and having national guidance has led to improved patient care overall (106; 158). As with the outpatient population, the increased use of technology may help avoid hypoglycemia (159).

Hypoglycemia has been associated with adverse cardiovascular outcomes, such as increased myocardial contractility, prolonged QT interval (possibly due to the rapid drop in potassium concentrations due to the increased circulating epinephrine and norepinephrine), ischemic electrocardiogram changes and repolarization abnormalities, angina, arrhythmias, increased inflammation, and sudden death, (51; 160-162). The mechanisms for the poor outcome have yet to be entirely understood. Still, hypoglycemia has been associated with increases in pro-inflammatory cytokines (TNFα, IL-1β, IL-6, and IL-8), markers of lipid peroxidation, acute changes in endothelial dysfunction with associated vasoconstriction, increased blood coagulability, cellular adhesion, and oxidative stress (163; 164).

Despite these observations, the direct causal effect of iatrogenic hypoglycemia on outcome is still debatable. Kosiborod et al. reported that spontaneous hypoglycemia, but not insulin–induced hypoglycemia, was associated with higher hospital mortality (152). Similarly, another study among 31,970 patients also reported that hypoglycemia is associated with increased in-hospital mortality. Still, the risk was limited to patients with spontaneous hypoglycemia and not to patients with drug-associated hypoglycemia (165). These studies raise the possibility that hypoglycemia, like hyperglycemia, despite the biochemical and other changes described, is a marker of disease burden rather than a direct cause of death.

RECOMMENDATIONS FOR MANAGING HYPERGLYCEMIA IN THE HOSPITAL ENVIRONMENT

Knowledge of Diabetes Management Amongst Medical Staff

The burden on inpatient diabetes falls most frequently on junior medical staff, who often have little or no specialist diabetes training. As such, it is perhaps unsurprising that errors occur. In the UK, a survey of junior doctors showed that unlike other commonly encountered medical conditions, such as acute asthma or angina, their knowledge about and confidence in managing diabetes was significantly lower (166). In 2019, this was also shown in a multicenter study from the US – with the major difference being that whilst most staff felt confident and comfortable managing diabetes, when challenged on how to manage certain situations, and in particular identifying glucose targets for those who were critically ill or the threshold for defining hypoglycemia, their confidence was far higher than their knowledge – a potentially devastating combination (167). Given the high prevalence of diabetes amongst hospital inpatients, essential diabetes management should be part of mandatory training. However, studies have found that despite the implementation of training programs, structured staff education has not shown to be of significant benefit in terms of improved patient outcomes (168; 169)

Management of Inpatient Hyperglycemia in the ICU

Insulin is the best way to control hyperglycemia in the inpatient setting, especially in critically ill patients. A variable-rate intravenous insulin infusion is the preferred method to achieve the recommended glycemic target (ADA Standards of Care 2025). The short half-life of intravenous insulin

makes it ideal in this setting because it allows flexibility in the event of unpredicted changes in an individual's health, medications, and nutrition.

When someone is identified as having hyperglycemia (blood glucose ≥180 mg/dl [≥10.0 mmol/l]), a variable rate intravenous insulin infusion should be started to maintain blood glucose levels <180 mg/dl (<10.0 mmol/l). A variety of intravenous infusion protocols are effective in achieving glycemic control with a low rate of hypoglycemic events and in improving hospital outcomes (73; 86; 113; 121; 170-174). A proper protocol should allow flexible blood glucose targets to be modified based on the individual's clinical situation. Further, it should have clear instructions about the blood glucose threshold for initiating an insulin infusion and the initial rate. The appropriate fluids should also be prescribed. It should be validated to avoid hyperglycemia if adjusted too slowly and hypoglycemia if adjusted too fast. Accurate insulin administration requires a reliable infusion pump that can deliver the insulin dose in increments of 0.1 units per hour (138; 172).

There is no ideal insulin protocol for managing hyperglycemia in the critically ill patient. In addition, no clear evidence demonstrates the benefit of one protocol/algorithm versus any other (138). Implementing any of these algorithms requires close follow-up by the nursing staff and is prone to human errors. Some institutions have developed computerized protocols that can be implemented to avoid errors in dosing (138; 175-179). Essential elements that increase protocol success of continuous insulin infusion are: 1) rate adjustment considers the current and previous glucose value and the current rate of insulin infusion, 2) rate adjustment considers the rate of change (or lack of change) from the previous reading, and 3) frequent glucose monitoring (hourly until stable glycemia is established, and then at least every 2 – 3 hours) (138; 171; 180-182).

Several computer-based algorithms aiming to direct the nursing staff in adjusting the insulin infusion rate have become commercially available (175-177; 179; 183). Retrospective cohorts and controlled trials have reported a more rapid and tighter glycemic control with computer-guided algorithms than standard paper form protocols in ICU patients (176; 184), as well as lower glycemic variability than patients treated with the standard insulin infusion regimens. Despite differences in glycemic control between insulin algorithms, another study showed no difference between computerized protocols versus conventional glucose control (128). Thus, most insulin algorithms appear to be appropriate alternatives for managing hyperglycemia in critically ill patients, and the choice depends upon the physician's preferences, staffing availability, and cost considerations. As mentioned, the increasing implementation of available technology, in particular the use of closed loops should improve the management of dysglycemia over the coming years (185-187).

MANAGING HYPERGLYCEMIA IN THE NON-ICU SETTING

Subcutaneous insulin is the preferred therapeutic agent for glucose control in those admitted to non-ICU settings under general medicine and surgery. A recent study suggested that the use of bolus correction doses of subcutaneous insulin ("subcutaneous sliding scale insulin" (SSI)) is an acceptable way of controlling dysglycemia, particularly in those whose admission glucose levels were <180 mg/dl (10 mmol/l) (188; 189). However, many studies do not agree and advocate against using this method as the only way to control glucose levels because it results in undesirable hypoglycemia and hyperglycemia or inadequately controls dysglycemia (109; 190-193). It has become evident in recent years that the use of scheduled subcutaneous insulin therapy with basal (e.g.

glargine, detemir or degludec) once daily or with intermediate-acting insulin (NPH) given twice daily alone or in combination with short (regular) or rapid-acting insulin (lispro, aspart, glulisine) prior to meals is effective and safe for the management of most patients with hyperglycemia and diabetes (20; 108; 194).

The basal-bolus (prandial) insulin regimen is considered the physiologic approach as it addresses the three components of insulin requirement: basal (what is required in the fasting state), nutritional (what is needed for peripheral glucose disposal following a meal), and supplemental (what is necessary for unexpected glucose elevations, or to dispose of glucose in hyperglycemia (195).

A prospective, randomized multi-center trial compared the efficacy and safety of a basal/bolus insulin regimen with basal-bolus regimen and SSI in people with type 2 diabetes admitted to a general medicine service (139). The use of a basal-bolus insulin regimen improved blood glucose control more than the subcutaneous sliding scale alone. A blood glucose target <140 mg/dl (<7.8 mmol/l) was achieved in 66% of those in the glargine plus glulisine group and 38% in the sliding scale group (139). The incidence of hypoglycemia, defined as a BG <60 mg/dl (<3.3 mmol/l), was less than 5% in those treated with basal-bolus or SSI. A different study on general surgery inpatients also compared the efficacy and safety of a basal-bolus regimen to SSI in those with type 2 diabetes (71). The basal-bolus regimen resulted in a significant improvement in glucose control and a reduction in the frequency of the composite of postoperative complications, including wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia.

Multi-dose human NPH and regular insulin have been compared to basal-bolus treatment with insulin analogs in an open-label, controlled, multicenter trial in 130 medical admissions with type 2 diabetes (196). This study found that both treatment regimens significantly improved inpatient glycemic control with a glucose target of <140 mg/dl (<7.8 mmol/l) before meals and no difference in the rate of hypoglycemic events. Thus, a similar improvement in glycemic control can be achieved with either basal-bolus therapy with insulin analogs or with NPH/regular human insulin in people with type 2 diabetes.

Most people in the hospital have reduced caloric intake due to a lack of appetite, medical procedures, or surgical intervention. In the Basal Plus trial, people with type 2 diabetes who were treated with diet, oral antidiabetic agents, or low-dose insulin (≤ 0.4 unit/kg/day) prior to admission were randomized to receive a standard basal-bolus regimen with glargine once daily and glulisine before meals or a single daily dose of glargine. In addition, supplemental doses of glulisine were administered for correction of hyperglycemia (>140 mg/dl [>7.8 mmol/l]) per sliding scale (197). This study reported that the basal approach resulted in similar improvement in glycemic control and the frequency of hypoglycemia compared to a standard basal-bolus regimen (197). Thus, in insulin-naive individuals or those receiving low-dose insulin on admission, as well as those with reduced oral intake, the use of a basal plus regimen is an effective alternative to basal-bolus (108).

The recommended total daily insulin dose should start between 0.3 to 0.5 units per Kg (139; 147; 198; 199) for most people with diabetes. Starting doses greater than 0.6 – 0.8 units/kg/day have been associated with 3-fold higher odds of hypoglycemia than doses lower than 0.2 U/kg/day. In elderly individuals or those with impaired renal function, lower initial daily doses (≤ 0.3 units/kg) may lower the risk of hypoglycemia (200).

HOSPITAL USE OF NON-INSULIN THERAPY IN NON-CRITICAL CARE SETTINGS

Several other classes of non-insulin glucose-lowering agents have been tried in the hospital setting. However, most are not suitable for use. Metformin, while the first line for type 2 diabetes in the outpatient setting, may not be appropriate where there is any evidence of dehydration, renal impairment, or if intravenous contrast is due to be administered due to the risk of lactic acidosis or worsening of renal function (195). Despite the lack of robust evidence of benefit, it remains in everyday use in many countries (201). Thiazolidinediones are excellent at lowering glucose but are used rarely, and possibly inappropriately, in hospitalized patients because they take several weeks to reach their maximum effect, may precipitate heart failure, and may cause peripheral edema due to fluid retention (202-204).

Sulfonylureas work rapidly and are often the drugs of choice for worsening diabetes in an outpatient setting (205). They remain in everyday use in many countries, with up to 20% of inpatients with diabetes in the USA and UK remaining on them (140; 203). However, they increase the risk of hypoglycemia. There is data to show that they remain one of the most frequent causes of inpatient hypoglycemia, thus extending the length of hospital stay and increasing the risk of inpatient mortality (141; 206-208).

Oral glucose-lowering medication use is limited by the delay and unpredictability of onset of action, and there is also concern regarding the cardiovascular effects of sulfonylureas and the contraindication of metformin use in patients with renal or liver dysfunction (19; 209). Recent work using the sodium-glucose co-transporter 2 inhibitors for corticosteroid-induced hyperglycemia in acute exacerbation of chronic obstructive pulmonary disease (COPD) or used in COVID infections failed to demonstrate an improvement in outcomes (210; 211). Indeed, despite their clear benefits in the outpatient population with and without diabetes, robust evidence for the benefit of SGLT2i use in the inpatient population (in people with diabetes) is lacking (212; 213).

The use of oral antidiabetic agents was not recommended in previous guidelines because of the need for more safety and efficacy studies in the inpatient setting (20). However, increasing evidence indicates that treatment with dipeptidyl peptidase-4 (DPP4) inhibitors, alone or in combination with basal insulin, is safe and effective in general medicine and surgery with mild to moderate hyperglycemia (48). In a pilot study, general medicine and surgical inpatients with blood glucose between 140 and 400 mg/dl (7.8 – 22.2 mmol/l) treated with diet, oral antidiabetic drugs, or low-dose insulin (≤0.4 U/kg/day) were randomized to sitagliptin once daily, sitagliptin and basal insulin, or basal-bolus insulin (214). All groups received correction doses of lispro before meals and bedtime for blood glucose >140 mg/dl (>7.8 mmol/l). In those with mild-moderate hyperglycemia (<180 mg/dl [<10 mmol/l]), the use of sitagliptin plus supplemental (correction doses) or in combination with basal insulin resulted in no significant differences in mean daily blood glucose, frequency of hypoglycemia or the number of treatment failures compared to the basal-bolus regimen (214). The SITA-HOSPITAL trial, a multicenter, randomized controlled study in 279 general medicine and surgery individuals with type 2 diabetes previously treated with oral anti-diabetic agents or low-dose insulin (<0.6 U/kg/d), also reported similar glycemic control, hypoglycemia rate, hospital length-of-stay, treatment failures or hospital complications (including acute kidney injury or pancreatitis) between the combination of oral sitagliptin plus basal insulin to the more labor-intensive basal-bolus insulin regimen (215).

Analysis from prospective studies using DPP4-i in various inpatient situations with type 2 diabetes (T2D) reported that treatment with DPP4-i alone or with basal insulin suggested they were safe and lowered

glucose concentrations without increasing the risk of hypoglycemia (216; 217).

For people with type 2 diabetes hospitalized with heart failure, the ADA has recommended that the use of a sodium-glucose cotransporter 2 (SGLT2) inhibitor be initiated or continued during hospitalization and upon discharge if there are no contraindications and after recovery from the acute illness (218-221). In patients with acute heart failure, empagliflozin was well tolerated, resulting in significant clinical benefits, including heart failure readmissions and quality of life (221). However, SGLT2 inhibitors should be avoided in cases of severe illness, in people with type 1 diabetes, ketonemia, or ketonuria, and during prolonged fasting and surgical procedures. Proactive adjustment of diuretic dosing is recommended during hospitalization and/or discharge, especially in collaboration with a cardiology/heart failure consult team. The FDA has warned that SGLT2 inhibitors should be stopped three days before scheduled surgeries (4 days in the case of ertugliflozin) (222). This differs from the UK guideline, which states that these drugs should be omitted from the day before a procedure (223).

Staffing Levels in the Hospital

Inadequate levels of appropriately knowledgeable staff are a concern for patients with diabetes (224). An insufficient level of specialist diabetes staff is a factor that inhibits safe and optimal care (34). Recently, the UK JBDS group developed a simple calculator into which individual teams could enter data to calculate their staffing needs (49). That data showed the discrepancy between the number of people delivering care and the number of people that specialist teams felt was necessary to provide safe and effective care for five days or seven days per week. This was for senior medical staff, specialist nursing staff, dieticians, podiatrists, pharmacists and psychologists (49).

Glucose Monitoring in the Hospital

All patients admitted to the hospital with a diagnosis of diabetes and those with newly discovered hyperglycemia should be monitored closely (21). The frequency and method of monitoring and the schedule of the blood glucose checks will depend on the nutritional intake, patient treatment, and insulin schedule, as well as the ability of the individual to self-manage their diabetes (225). There is some controversy regarding the best method to monitor blood glucose. However, considering the convenience and wide availability of capillary point of care (POC) testing, we suggest this as the best approach if done with a monitoring device that has demonstrated accuracy (226-228). When using POC blood glucose meters, it is important to keep several things in mind. In particular, overall clinical conditions that might affect the POC value, such as hemoglobin level, perfusion, and medications, as well as the policy of the health care organization in guiding the patient and the staff on the use of POC devices or newer technologies.

Bedside point-of-care (POC) capillary glucose testing is usually ordered before meals and bedtime to assess glycemic control and adjust insulin therapy in the hospital (19; 228). However, this approach has been shown to fail to detect hypoglycemia, particularly nocturnal and asymptomatic hypoglycemia, which is a common scenario in the hospital setting (229; 230).

Continuous glucose monitoring (CGM) has increased over the last few years, helping to improve glycemic management in the ICU. The use of this technology was accelerated during the COVID pandemic, where the use of CGM meant that close contact with sick individuals was avoided using remote sensing (231-234). The use of CGM is questioned, with the accuracy of readings when dealing with hypoglycemia or in the operating room (235; 236). However, in general, most

studies have been associated with overall benefit (234; 237; 238).

CGM is reliable compared to point-of-care testing and laboratory values in the inpatient setting. It is currently being evaluated for managing ICU and general ward patients (159; 185; 235; 239-242). Studies have shown that CGM offers advantages over intermittent capillary monitoring in the ICU. CGM can help identify and prevent severe hyperglycemia and hypoglycemia by allowing for more rapid and accurate adjustments to insulin infusions compared to capillary blood glucose testing. Research has also demonstrated that CGM is better at detecting hypoglycemia, predominantly asymptomatic and nocturnal hypoglycemia, than capillary glucose testing (243; 244). Additionally, CGM is as safe and effective as standard care in hospitalized patients and can lead to a significant decrease in recurrent hypoglycemia events compared with standard point-of-care testing (243; 245). Regulatory approval for CGM use in hospitals is still pending, but consensus guidelines suggest that the use of CGM in the hospital setting has the potential to provide a better glycemic assessment than capillary glucose testing (Walia et al.; other, Endo Soc Guidelines). Furthermore, advanced technology in guiding insulin therapy using machine learning and artificial intelligence is being integrated more frequently into diabetes care (246). A proof-of-concept trial in patients with type 2 diabetes evaluated the efficacy and safety of a model-based reinforcement learning framework in titrating insulin dosing. After applying the intervention, the mean daily BG was lower by approximately 56 mg/dl (3 mmol/l) with no severe hypo- or hyperglycemia (247).

The American Diabetes Association (ADA) and UK JBDS recently recommended that people with diabetes who use a personal continuous glucose monitoring (CGM) device should be allowed to continue during hospitalization (48; 159; 248). Both organizations also recommend that confirmatory point-of-care (POC) glucose measurements be used for insulin dosing decisions, hypoglycemia assessment, and treatment.

A recent survey of inpatient teams across the UK showed significant variations in accessing and using technologies (249). These included networked glucose and ketone meters, and wearable diabetes technologies such as CGM, pumps, or closed loop systems. While almost two-thirds of respondents agreed that technology would help prevent hypoglycemia, there was a wide variety of specialist diabetes nursing or medical staff support available to help non-specialists, particularly on weekends or outside of regular working hours (249).

Medical Nutrition Therapy (MNT) in Hospitalized Patients with Diabetes

Medical nutrition therapy (MNT) is a key component of the comprehensive management of diabetes and hyperglycemia in the inpatient setting. Maintaining adequate nutrition is essential for glycemic control and to meet adequate caloric demands. Caloric demand in acute illness will differ from that in the outpatient setting. Achieving the proper nutritional balance in the inpatient setting is challenging. Anyone admitted to the hospital with diabetes or hyperglycemia should be assessed to determine the need for a modified diet to meet caloric demands.

The general approach to addressing MNT in the inpatient setting is usually based on expert opinions and patients' needs. Limited data exist regarding the best approach or method to achieve the ideal caloric supply. To determine the best approach, method, and caloric needs of their patients, providers should work closely with the nutrition professional.

All patients with diabetes or hyperglycemia should receive an individualized assessment. Most patients will generally receive adequate caloric

needs with 3 discrete meals daily. Further, the metabolic need for patients with diabetes is usually provided by 25 to 35 calories/kg, whereas some critically ill patients might require less than 15 to 25 calories/kg per day (250; 251). A consistent carbohydrate meal-planning system might help to facilitate glycemic control and insulin dosing in the inpatient setting. Most patients require 1,500-2000 calories daily with 12-15 grams of carbohydrates per meal (19). Ideally, the carbohydrates should come from low glycemic index foods such as whole grains and vegetables.

Those individuals unable to achieve these goals should be evaluated to determine the need for enteral or parenteral nutrition. Enteral nutrition is the second-best option after oral nutrition and should be preferred over parenteral nutrition in hospitalized individuals (252-254). There are several advantages of enteral feeding versus parenteral feeding, including low cost, low risk of complications, a physiologic route, less risk for gastric mucosa atrophy, and lower risk of infectious and thrombotic complications compared with the latter form of therapy (252-254). The benefit of parental nutrition has been documented in critically ill patients. However, some research has shown a detrimental effect on patients with diabetes and hyperglycemia. Parental nutrition should be considered only in patients who cannot receive enteral nutrition and should be coordinated with the institution's parenteral nutrition team. There has been guidance published in the surgical population on peri-operative nutrition, but the recommendations for people with diabetes is lacking because the literature remains scanty (251). A recent UK survey of diabetes teams showed no consensus on enteral feeding regimens (253). For those tube-fed, there were 3 main regimens: continuous 24-hour feeding, a single feed with one

break in 24 hours, or multiple feeds in 24 hours. In addition, there were multiple insulin regimens used: premixed insulin, isophane insulin, analog basal insulin, variable rate intravenous insulin, or basal-bolus insulin. None of these provided adequate glycemic control (253).

Enteral and parenteral nutrition can prevent the effects of starvation and malnutrition (252). Enteral nutrition over parenteral nutrition is preferred whenever possible due to a lower risk of infectious and thrombotic complications (254-256). Standard enteral formulas reflect the reference values for macro- and micronutrients for a healthy population and contain 1-2 cal/ml. Most standard formulas contain whole protein, lipids in the form of long-chain triglycerides, and carbohydrates. Standard diabetes-specific formulas provide low amounts of lipids (30% of total calories) combined with a high carbohydrate (257) content (55–60% of total calories); however, newer "diabetic" formulas have replaced part of carbohydrates with monounsaturated fatty acids (up to 35% of total calories) and also include 10-15 g/l dietary fiber and up to 30% fructose (257; 258).

"Diabetic" enteral formulas containing low-carbohydrate high–monounsaturated fatty acid (LCHM) are preferable to standard high-carbohydrate formulas in hospitalized patients with type 1 and type 2 diabetes (257; 258). In a meta-analysis of studies comparing relatively newer enteral LCHM formulas with older formulations, the postprandial rise in blood glucose was reduced by 18- 29 mg/dl [1.0-1.6 mmol/l] with the newer formulations (258). Table 4 depicts the composition of standard and diabetic-specific enteral formulas commonly used in hospitalized patients.

Table 4. Composition of Standard and Diabetic Specific Enteral Formulas Commonly Used in Hospitalized Patients in the USA					
	Calories (kcal/mL)	Carbohydrate (g/l)	Fat (g/l)	Protein (g/l)	Manufacture
Standard					
Jevity® 1.0 Cal	1.0	140	35	40	Abbott Nutrition
Nutren® 1.0	1.0	109	27	70	Nestle Nutrition
Osmolite® 1.2 Cal	1.2	158	39	56	Abbott Nutrition
Jevity® 1.2	1.2	169	39	56	Nestle Nutrition
Fibersource® HN	1.2	164	40	54	Nestle Nutrition
Isosource® 1.5	1.5	176	60	68	Nestle Nutrition
Jevity® 1.5	1.5	216	50	64	Nestle Nutrition
Diabetes specific formula					
Glucerna® 1.0 Cal	1.0	75	54	50	Abbott Nutrition
Nutren® Glytrol®	1.0	100	48	45	Nestle Nutrition
Glucerna® 1.2 Cal	1.2	114	60	60	Abbott Nutrition
Diabetisource®	1.2	100	59	60	Nestle Nutrition
Glucerna® 1.5	1.5	133	75	83	Abbott Nutrition

The UK Joint British Diabetes Societies has updated its guidelines for the management of diabetes in enterally fed people (259).

Corticosteroid Therapy – Impact on Blood Glucose

Steroid use in hospitalized patients is common. A single-center cross-sectional study showed that 12.8% of all the people in the hospital were on glucocorticoids (260). Steroids may be administered by various regimes and at variable doses. A single daily dose of steroid (e.g., prednisolone/prednisone) in the morning may be the most standard mode of administration (205; 260-262). Limbachia et al. showed that, in susceptible individuals, steroid use will often result in a rise in blood glucose by late morning that continues through to the evening (263). Overnight, the blood glucose generally falls back to baseline levels by the following day. They also showed the differential effects between different steroid types, with oral or IV dexamethasone or methylprednisolone leading to higher glucose excursions than prednisolone or hydrocortisone (262). Thus, treatment should be tailored to treating the hyperglycemia while avoiding nocturnal and early morning hypoglycemia. Multiple daily doses of steroid, be it intravenous hydrocortisone or oral dexamethasone, can cause a hyperglycemic effect throughout the 24-hour period. It may be, however, that a twice-daily premixed or basal-bolus regimen may need to be started if oral medication or once-daily insulin proves insufficient to control hyperglycemia (205). Close attention will therefore need to be paid to blood glucose monitoring, and early intervention may be necessary.

Glucose levels in most individuals can be predicted to rise approximately 4 to 8 hours following the administration of once-daily oral steroids and sooner following the administration of intravenous steroids. Again, capillary blood glucose monitoring is paramount to guide appropriate therapeutic interventions. Conversely, glucose levels may improve to pre-steroid levels 24 hours after intravenous steroids are discontinued. When oral steroids are weaned down, the glucose levels may decline in a dose-dependent fashion, but this may not occur, particularly in those with pre-existing undiagnosed diabetes.

At the commencement of steroid therapy, or for those already on a supraphysiological dose of corticosteroid, capillary blood glucose testing should occur before meals and at bedtime, in particular before lunch or evening meal, when the hyperglycemic effects of a morning dose of steroid are likely to be greatest (205; 262).

Subcutaneous insulin using a basal or multiple daily injection regimen will likely be the most appropriate choice for most patients to achieve glycemic control in the event of hyperglycemia. While the UK has advocated for short-acting sulfonylureas (205), the morning administration of basal human insulin may closely fit the glucose excursion induced by a single morning dose of oral steroid. Basal analog insulin may be appropriate if hyperglycemia is present for more prolonged periods. However, if long-acting insulin analogs are used in this context, care should be taken to identify and protect against hypoglycemia overnight and in the early morning. Subsequent titration of the insulin dose may be required to maintain glucose control in the face of increasing or decreasing the steroid dose.

When a patient is discharged from the hospital on steroid therapy, a clear strategy for managing hyperglycemia or potential hyperglycemia and the titration of treatment to address the hyperglycemia should be communicated to the community diabetes team and primary care team. Patients who commenced on steroids as inpatients and were discharged after a short stay with the intention of continuing high-dose steroids should receive standard diabetes education, encompassing the risks associated with hyperglycemia and hypoglycemia.

Closed Loop Technology

Several organizations have recommended that people who are well enough to do so should continue to use their insulin pumps in hospitals (108; 109; 240; 264). However, only a few recent studies have reported using closed-loop systems, also referred to as the artificial pancreas or automated insulin delivery systems, in hospitalized inpatients. Small randomized trials have reported good efficacy with improved time in target and lower mean daily blood glucose without an increased rate of hypoglycemia in the ICU (265-267) and non-ICU settings (268-271). However, some of these studies were done in those with type 2 diabetes (268; 270). In one non-ICU study, the time in the target range between 100-180 mg/dl (5.6-10.0 mmol/l) was reported as 59.8% in patients using the closed-loop technology compared to 38.1% with standard subcutaneous insulin regimen (269).

Similarly, a closed-loop study in patients receiving nutritional support also reported higher time in target glucose (68% vs 36.4%) and lower mean glucose values (153 vs 205 mg/dl [8.5-11.4 mmol/l]) compared to a standard insulin regimen (270). As with the use of CGM in the hospital, treatment with artificial pancreas is still experimental, and larger studies are needed to prove its safety and efficacy in ICU and non-ICU settings. Further challenges lie ahead because of the unfamiliarity of these systems, with non-specialist staff the primary carers for people with diabetes.

The ADA has recommended that insulin pumps or automated insulin delivery (closed-loop) systems be continued for hospitalized individuals with diabetes when clinically appropriate. Confirmatory POC blood glucose measurements should be used for insulin-dosing decisions and for assessing and treating hypoglycemia. However, this depends on the availability of required supplies and resources, proper training, ongoing competency assessments, and the implementation of institutional diabetes technology protocols (48).

As with the CGM, those who are well and can self-manage can look after their devices and diabetes.

However, in those who are unwell or incapacitated, the systems must be disengaged from automatic and set to 'manual' mode to allow the diabetes teams to help manage the diabetes. The systems may not also be able to cope with the acute changes that occur in the hospital, including (but not limited to) change in oral carbohydrate intake, the use of glucocorticoids or other medications inducing insulin resistance; peri-operative use, nausea and vomiting; enteral or parenteral nutrition. Once again, the use of 'manual' mode is recommended in these situations, and the diabetes is managed in conjunction with the specialist diabetes team.

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