Consensus and Guideline

Expert consensus on the glycemic management of critically ill patients

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Introduction

The incidence of hyperglycemia is 40–60% in critically ill patients and is up to 60–80% in those who have undergone cardiac surgery.[1] The results of an epidemiological study in the United States showed that 28.6% of diabetic patients and 9.3% of non-diabetic patients had elevated mean daily glucose on the day of ICU admission.[2] In critically ill patients, elevated blood glucose is primarily the result of stress, and stress-induced hyperglycemia is an independent risk factor associated with prognosis, regardless of a previous diagnosis of diabetes. Nutritional therapy has become an integral treatment option for patients in the ICU,[3,4] though nearly 30% of patients with enteral nutrition and 44–50% with parenteral nutrition (PN) experience elevated glucose.[5,6] Intensive insulin therapy (IIT) is an important treatment for controlling hyperglycemia in critically ill patients, but it also carries a corresponding risk of hypoglycemia, with the incidence of relative hypoglycemia (a decrease in glucose ≥30% below prehospital admission levels) and mild hypoglycemia (<3.9 mmol/L) reaching 34–45% .[7,8]

Hyperglycemia and relative hyperglycemia are independent risk factors for increased mortality among critically ill patients[9,10] and an important predictor of poor short- and long-term outcomes among hospitalized patients, including increased mortality, length of hospital stay, and need for care after discharge.[11–13] Hypoglycemia also increases the risk of death among critically ill patients.[7,8,14–17] Glycemic variability is an independent risk factor for the increased mortality of critically ill patients and can be used to assess illness severity.[18,19] The 2016 ASPEN guidelines indicate that the selection of appropriate nutrients and meticulous glycemic control contribute to improved outcomes among critically ill patients.[4] Thus, it is important to strengthen the glycemic management of critically ill patients.

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Table 1
Recommendation levels according to the GRADE method.

Levels	Opinion and description of the recommendation	Quality of evidence
Grade 1+	Strong recommendation	High-quality evidence
Grade 2+	Weak recommendation	Low-quality evidence
Expert's opinion	Suggested in expert's opinion	Insufficient evidence
Grade 2−	Weak recommendation	Low-quality evidence
Grade 1−	Strong recommendation	High-quality evidence

GRADE: Grading of recommendations assessment, development, and evaluation.

There is controversy about how best to manage glycemia among critically ill patients in China, and suboptimal management remains an issue in clinical practice. To strengthen and standardize clinical practice, an expert working group on glycemic management composed of Chinese experts in critical medicine conducted five rounds of discussion to summarize 26 important statements about glycemic management in critically ill patients. This was six parts and included research progress worldwide while considering the current situation in China. A consensus was established to provide guidance and reference opinions for the glycemic management of critically ill patients to optimize clinical practice. Clinical issues were developed according to the Patient, Intervention, Comparison, and Outcome (PICO) principles. The quality of evidence and strength of recommendations were evaluated using grading of recommendations assessment, development, and evaluation (GRADE). The strength of each recommendation was collectively discussed and voted on by all members of the working group, and only included if it sustained ≥80% of the vote. Strong evidence was defined as including at least one multicenter, randomized, double-blind controlled study with no apparent design issues and data excursions or considered strong evidence by systematic review while weak evidence was defined as randomized control trial, case-control, or observational cohort studies with significant design defects and data excursions, or considered weak evidence by systematic review. If the evidence was insufficient, expert opinions were adopted. Recommendations were classified as "strong recommendations" or "weak recommendations" [Table 1]. Strong recommendations were expressed as "Recommend…" while weak recommendations were expressed as "Suggest…."

Overview of the Diagnosis and Pathophysiology of Hyperglycemia and Hypoglycemia in Critically Ill Patients

Physiological functions of blood glucose

Many biochemical reactions take place in human cells, transforming the energy in food and activating various physiological systems, including muscle activity, glandular secretion, and the maintenance of nerve membrane potential. Energy substrates, such as carbohydrates, fats, and proteins, are oxidized in cells to release energy. Carbohydrates are absorbed by the digestive tract, producing glucose, fructose, and galactose, and most fructose and almost all galactose are rapidly converted into glucose by the liver. Blood glucose refers to glucose in the blood, which is broken down by aerobic oxidation or glycolysis to produce energy. Human blood glucose levels are relatively constant and are maintained at 3.89–6.11 mmol/L.

Regulatory mechanisms of blood glucose

In humans, plant starch, animal glycogen, and maltose contained in food are digested into monosaccharides, which are absorbed by the small intestine and transported to the liver through the portal vein to participate in glucose metabolism. The absorption, decomposition, and metabolism of nutrients and gluconeogenesis are the basis for stabilizing blood glucose. The metabolism of glucose, fat, and amino acids and the coordinated metabolic function of various organs and tissues are also critical to the stabilization of blood glucose levels. The balance of blood glucose levels is regulated by hormones such as insulin, glucagon, epinephrine, and glucocorticoids. Congenital enzymatic defects, imbalanced hormones, and functional organs impairment can destabilize blood glucose levels.

Diagnosis, pathophysiology, and the effects of hypoglycemia in critically ill patients

Low blood glucose has various causes and is called as hypoglycemia when glucose levels in blood are <2.8 mmol/L (<3.9 mmol/L in diabetic patients) along with particular signs and symptoms.[20] The incidence of hypoglycemia is 18–65% in critically ill patients[14] and the mortality is approximately 35.4–50.2% in patients with severe hypoglycemia.[7,21] Hypoglycemia is independently associated with increased mortality in critically ill patients and the risk increases with time and number of hypoglycemic episodes.[7] Hypoglycemia pathogenesis is complex, and the high-risk factors include IIT, interruption of caloric intake without adjustment of insulin infusion, hepatic and renal failure, and continuous renal replacement therapy. Hypoglycemia is also related to blood glucose dysregulation, which reduces the blood glucose supply under stress conditions.

The main reactions of the body to hypoglycemia include increased endogenous glucose production through glycogenolysis, gluconeogenesis, and eating behavior. Endogenous insulin secretion decreases when human blood glucose levels fall <4.6 mmol/L. A blood glucose level <3.8 mmol/L promotes pancreatic α cells to secrete endogenous glucagon, which induces glycogenolysis and gluconeogenesis. As blood glucose continues to drop, adrenaline secreted from the adrenal medulla directly promotes glucose release from the liver, limits insulin secretion, reduces tissue sensitivity to insulin, and mobilizes the use of glycogenic substrates, such as lactic acid, amino acids in muscles, and glycerol in fat.[22] Severe hypoglycemia is uncommon during the early stages of the disease because of the defensive physiological mechanisms described above. As the disease continues, however, glucagon release becomes impaired, and adrenaline levels become insufficient as the sympathetic adrenal

reaction becomes activated. This increases the risk of severe hypoglycemia that can lead to coma, hemiplegia, and/or epileptic seizures, and ultimately, permanent neurological dysfunction. Numerous studies have demonstrated that hypoglycemic episodes increase the risk of fatality and length of hospital stay.[7]

Hyperglycemia in critically ill patients

Etiology and diagnosis of hyperglycemia

Hyperglycemia in critically ill patients is primarily the result of stress. Trauma, surgery, hypoxemia, infection, and other factors put the body in a very stressful state, resulting in abnormal stress-associated hormone secretion, insufficient insulin secretion, and the production of numerous inflammatory cytokines.[23,24] Fluid infusion and nutritional therapy can also directly affect blood glucose and aggravate the hyperglycemia status of patients.

A consensus on the criteria for the diagnosis of stress-induced hyperglycemia has not yet been established. Currently, stress-induced hyperglycemia is diagnosed using two or more spot blood sugar tests after admission and is defined as a fasting blood glucose ≥126 mg/dL or a random blood glucose ≥200 mg/dL. The determination of glycosylated hemoglobin (HbA1c) may help to identify patients with diabetes who have >6.5% HbA1c, while most of those with stress-induced hyperglycemia have <6.5% HbA1c. This method can identify approximately two-thirds of patients compared with rapid glycemic testing.[25,26]

Management of herglycemia

Stress-induced hyperglycemia greatly affects the outcome of critically ill patients and should be considered an abnormal state of glycemic metabolism. Clinicians must monitor stress-induced hyperglycemia by eliminating stressors and individualizing glycemic control to avoid complications.

Blood Glucose Monitoring in Critically Ill Patients

Pathologic stress often causes blood glucose abnormalities such as hyperglycemia, hypoglycemia, and increased glycemic variability in critically ill patients, leading to increased complications and poor outcomes. Thus, it is necessary to monitor, manage, and control blood glucose levels appropriately to prevent hypoglycemia-related adverse events. The safety and accuracy of bedside glucose monitoring methods are critical.

Question 1: Which method is recommended to monitor blood glucose in critically ill patients?

Statement 1: If an arterial catheter is available, arterial blood is preferred to monitor blood glucose in critically ill patients. If no arterial catheter is available, it is recommended that blood samples should be taken from a venous catheter (Grade 2+, weak recommendation). Continuous glucose monitoring (CGM) can be used to monitor blood glucose in critically ill patients with large blood glucose excursions (Grade 2+, weak recommendation).

Rationale: In critically ill patients, the sampling priority for glucose monitoring is arterial > venous > capillary.[27] A prospective observational study[28] found that the accuracy of

arterial blood glucose values (69.9% and 76.5% with a glucose meter and a blood gas analyzer, respectively) was higher than capillary blood glucose values (56.8% and 56.8%, respectively). The accuracy of capillary blood glucose values was only 26.3%, and the accuracy of arterial blood glucose values measured with a glucose meter or a blood gas analyzer was 55.6% and 64.9%, respectively. The World Health Organization (WHO) adopted venous blood glucose values as the diagnostic criteria for diabetes. Frequent venous blood sampling is not acceptable among critically ill patients, but blood samples may be drawn from a venous catheter, understanding that intravenous infusion of a glucose-containing solution may result in inaccurate blood glucose measurements. Capillary blood samples can lead to significant errors in glucose measurement compared with venous and arterial blood samples.[29] Capillary blood samples (needle prick) are indicated for critically ill patients with a relatively mild condition, no edema of the extremities, and no invasive arterial blood pressure monitoring, but are not indicated for critically ill patients.

Real-time CGM provides continuous, complete, and reliable full-day glucose measurements to help characterize trends.[30] In recent years, the accuracy and reliability of CGM in critically ill patients have also been assessed in several studies,[31–33] and a systematic analysis[34] found that they had small sample sizes, high heterogeneity, and low evidence.[30] Compared with standard glycemic monitoring methods, the CGM system has the potential to improve glycemic control in critically ill patients but requires technical improvements or integration with appropriate sensors. One study[35] found that a fully automated closed-loop glucose control system incorporating CGM and computer-assisted insulin infusion was safe and reliable, reducing the incidence of hypoglycemia and shortening the time required to reach the blood glucose target in critically ill patients.

Question 2: What are the factors required to improve the accuracy of blood glucose monitoring?

Statement 2: An arterial blood gas analyzer monitors arterial blood glucose more accurately than a glucose meter (Grade 2+, weak recommendation).

Rationale: While quantifying venous blood glucose levels, an automated biochemistry instrument is the gold standard for measuring blood glucose, but this method is time-consuming. Thus, blood gas analyzers or glucose meters are commonly used in the ICU. However, it is important to determine which method is the most accurate to monitor the blood glucose for critically ill patients. A systematic analysis of 21 studies[36] found that a blood gas analyzer or glucose meter measures arterial blood glucose more accurately than capillary blood glucose (odd ratios[ORs]=0.04 and 0.36, respectively, P <0.01). The study also found that an arterial blood gas analyzer provides a more accurate measurement of arterial blood glucose than a glucose meter (P=0.02), and a glucose meter measures arterial blood glucose more accurately than capillary blood glucose (P < 0.001). At low blood glucose levels (<4.5 mmol/L), the rate of error for assessing arterial blood glucose using a blood gas analyzer is low (OR=1.86 for arterial blood glucose, P=0.15; OR=1.84 for capillary blood glucose, P=0.03; OR=2.33 for arterial blood glucose, P=0.02). Factors affecting capillary glucose levels include the use of vasopressors, peripheral edema, peripheral hypoperfusion, high partial oxy-

gen pressure, hematocrit (Hct) <25% or >60%, and severe dehydration.[29,36,37]

Question 3: How often is blood glucose monitored?

Statement 3: We suggest that the interval between glucose monitorings should not be longer than 1 h for newly admitted critically ill patients or those who are critically ill and on continuous insulin infusion until glucose levels and the rate of insulin injection are stabilized (Grade 2+, weak recommendation).

Rationale: The frequency of glucose monitoring is closely related to hyperglycemia, hypoglycemia, and glycemic variability, which are the independent risk factors for fatality and length of hospital stay; however, the optimal frequency of glucose monitoring remains unknown. According to published glycemic control protocols,[38,39] including the VISEP[40] and GLUCONTROL studies,[41] blood glucose is generally monitored hourly following the initiation of insulin therapy and then once every 4 h after blood glucose levels are maintained within the set target range and the patient's clinical condition is stabilized. In these studies[38–41] the measurement of blood glucose every 1–4 h resulted in a >10% incidence of hypoglycemia. When blood glucose is unstable, prolonged measurement intervals increase the risk of not detecting hypoglycemia. Thus, blood glucose should be monitored at least once per hour in critically ill patients on routine insulin therapy.

A retrospective study of 4588 critically ill patients with 6069 insulin infusions found a median delay between hourly glucose measurements of 21.8 min (interquartile range [IQR]: 12.2–29 min) following hypoglycemia.[42] A Monte Carlo simulation of glucose monitoring in 100 patients with a 200 h follow-up at intervals of 15 min, 1 h, and 2 h showed that glycemic control in critically ill patients was ideal at glucose measurement intervals of no longer than 1 h and optimal at an interval of 15 min.[43] However, frequent blood glucose monitoring is time and staff intensive. Thus, we recommend intervals of ≤1 h for newly admitted critically ill patients and those who are critically ill and on continuous insulin infusion therapy and increasing the intervals to every 2–4 h when glucose levels and insulin injection rates are stabilized. If hypoglycemic episodes occur, blood glucose should be monitored every 15 min until blood glucose levels stabilize.

Question 4: Are indicators such as glycosylated hemoglobin (HbA1c) useful for monitoring blood glucose in critically ill patients?

Statement 4: We suggest routinely measuring HbA1c upon admission to the ICU (Grade 2+, weak recommendation).

Rationale: HbA1c levels are positively correlated with blood glucose and represent the average amount of glucose in the body 4–12 weeks before disease onset. Increased HbA1c levels indicate the presence of elevated blood glucose levels. Long-term hyperglycemia has a strong impact on the body, and the resulting metabolic and inflammatory imbalances affect many systems, including immunity.[44] Elevated blood glucose levels are an important measure of the development, progression, and outcomes of cerebrovascular disease in patients with diabetes.[45] Meanwhile, cardiovascular events and all-cause mortality increase by 20–30% for every 1% increase in HbA1c, and these associations are not affected by diabetes.[46]

In critically ill patients, HbA1c is used to identify stress-induced hyperglycemia and HbA1c levels reflect both the degree of endothelial damage and patient outcomes.[47] In critically ill patients undergoing emergency surgery, HbA1c levels on the day of surgery are highly consistent with preoperative levels and may thus be used as a prognostic index.[48] Patients with sepsis and HbA1c >6.5% develop severe hepatic and renal dysfunction and have a higher mortality rate within 72 h of admission.[49] Thus, in addition to measuring blood glucose levels, HbA1c levels should be quantitated in critically ill patients upon admission to the ICU to fully assess the premorbid metabolic status of patients, which has important clinical significance for predicting patient outcomes.

Question 5: Is the coefficient of variation for blood glucose a useful measure in critically ill patients?

Statement 5: We suggest monitoring the coefficient of variation for blood glucose (GLUcv) in critically ill patients (Grade 2+, weak recommendation).

Rationale: The coefficient of variation for blood glucose refers to swings in blood glucose levels over a certain time and can reflect dynamic changes. The blood glucose difference (GLUdif), average blood glucose value (GLUave), and standard deviation of blood glucose (GLUsd) are calculated using the initial glucose value and multiple glucose values at a given time point of treatment, and the coefficient of variation for blood glucose is calculated as $GLUcv = GLUsd \times 100/GLUave$.[50]

Multiple studies indicate that the higher the coefficient of variation for blood glucose, the higher the mortality of critically ill patients, independent of hypoglycemia, disease severity, and comorbidities.[50–52] The coefficient of variation for blood glucose is also closely associated with disease complications among critically ill patients, including shock and the use of renal replacement therapy, possibly because hyperglycemia and hypoglycemia are the independent risk factors for mortality.[53] In patients with stroke and brain injury, high variation in blood glucose levels during long-term hypothermia therapy are predictors of poor nervous system outcomes and mortality.[54] Sepsis patients with blood glucose differences >65 mg/dL on the day of admission are at increased risk of 30-day mortality. This was observed among non-diabetic but not diabetic patients.[18] Patients with low variability or even slightly high blood glucose may have better outcomes than those under strict glycemic control but with high blood glucose variability. It is recommended that an insulin regimen be developed to manage hyperglycemia among critically ill patients to achieve appropriate glycemic control and minimize variability.[55] Attention should be paid to changes in absolute glucose levels and blood glucose variability to minimize glycemic swings and reduce fatality.

Target Blood Glucose Levels among Critically Ill Patients with Various Diseases

Glycemic control among diabetic and non-diabetic critically ill patients

Some diabetes patients have chronically high blood glucose levels, and the mechanism by which they regulate glucose metabolism differs from that of non-diabetic patients.[56] Especially among patients with severe diabetes, hyperglycemia may have different biological and clinical significance.[57] Thus, hy-

perglycemia should be controlled differently among critically ill patients with and without diabetes.

Question 6: Within what range should blood glucose levels be controlled in non-diabetic critically ill patients?

Statement 6: We suggest maintaining blood glucose levels at 6.1–7.8 mmol/L in non-diabetic critically ill patients (Grade 2+, weak recommendation).

Rationale: Among non-diabetic patients, ICU mortality increases as average glucose levels rise. In 2005, a descriptive case-control study from the Mayo Medical Center confirmed that in non-diabetic critically ill patients, blood glucose levels were >8.0 mmol/L for a longer period in non-survivors than in survivors.[58] In 2013, Krinsley et al.[61] retrospectively analyzed blood glucose levels and outcomes in nearly 45,000 critically ill patients with and without diabetes and showed that an average glucose level of 4.4–7.8 mmol/L was independently associated with lower mortality, while average glucose >7.8 mmol/L was associated with higher mortality. In 2015, a retrospective study confirmed that the maintenance of blood glucose levels at 3.9–7.8 mmol/L for >80% of the time was associated with higher survival of critically ill patients without diabetes.[59] However, excessively strict glycemic control does not benefit critically ill patients. In a prospective multicenter RCT study (NICE-SUGAR), patients in the intensive glycemic control group (4.5–6.0 mmol/L) had a 2.6% increased risk of 90-day mortality (OR=1.14, 95% confidence interval[CI]: 1.02–1.28; P=0.00) and a 6.3% higher incidence of severe hypoglycemia ($P < 0.001$) than those in the regular glycemic control group (≤10.0 mmol/L), and there was no advantage to intensive glycemic control in the diabetes and non-diabetes subgroups.[60]

Question 7: How should blood glucose levels be controlled in critically ill patients with diabetes?

Statement 7: We suggest less strict glycemic control (6.1–11.1 mmol/L) for critically ill patients with diabetes (Grade 2+, weak recommendation).

Rationale: Critically ill patients with diabetes tolerate higher blood glucose levels better than non-diabetic patients; however, most studies of specific blood glucose levels were retrospective. A study conducted in 2008 found no apparent linear relationship between time-weighted glucose levels and the mortality of patients with diabetes, but the cut-off value associated with increased mortality was 11.1 mmol/L.[57] In 2013, Krinsley et al.[61] showed that diabetic patients with an average glucose level >6.1 mmol/L had lower mortality than those with an average level of 4.4–6.1 mmol/L; however, when the average glucose level exceeded 11.1 mmol/L, mortality increased. Notably, critically ill patients with diabetes are more likely to develop hypoglycemia than non-diabetic patients and this can increase the risk of mortality by nearly threefold.[61–63] Thus, close monitoring of glycemic control is particularly important.

Glycemic management among patients with severe brain injury (SBI)

SBI primarily includes traumatic brain injury (TBI) and stroke (hemorrhagic and ischemic). Hyperglycemia is a common complication of SBI because many stroke patients have diabetes or are in the prediabetic state, and those with SBI are more likely to develop stress-related hyperglycemia. Numerous studies have demonstrated that hyperglycemia is an independent risk factor for worsening brain injury, poor clinical outcomes, and high mortality.[64–66]

Question 8: Do SBI patients require glucose or glycosylated hemoglobin screening?

Statement 8: For SBI patients without a history of diabetes, we suggest measuring fasting glucose and glycosylated hemoglobin levels as early as possible to screen for diabetes or the pre-diabetic state (Grade 2+, weak recommendation).

Rationale: Epidemiological investigations indicate that stroke is closely related to abnormal glucose metabolism; 68.7–77% of stroke patients have hyperglycemia, 14–35% have a history of diabetes, 16–24% are newly diagnosed with diabetes, and 21–24% have abnormal glucose tolerance.[67,68] For stroke patients with no history of abnormal glucose metabolism, blood glucose monitoring, fasting blood glucose, and glycosylated hemoglobin (HbA1c) measurements should be performed as early as possible to ensure early detection of diabetes or the prediabetic state.[69] A retrospective multicenter analysis of 2133 patients found a higher risk of death in the high HbA1c group (HbA1c ≥6.5%) than the relative normal group of patients with recessive diabetes or pre-diabetes (HbA1c 5.02% to 5.38%).[70]

Question 9: What is the goal for glycemic control of SBI patients?

Statement 9: In SBI patients, an intensive insulin regimen aiming at reaching a blood glucose level of 4.4–6.0 mmol/L is not recommended (Grade 1−, strong recommendation). Instead, the suggested blood glucose level is 6.1–10.0 mmol/L (Grade 2+, weak recommendation).

Rationale: In several retrospective studies and randomized controlled trials (RCTs), mortality increased as blood glucose levels increased in SBI patients.[64–66] Compared to conventional glycemic control, IIT does not improve long-term neurological outcomes or reduce ICU or hospitalization-associated mortality but does increase the incidence of hypoglycemia and the use of clinical resources.[71–75] In a subgroup analysis of 391 critically ill neurology patients enrolled in a multicenter, large RCT study in 2015,[74] no differences were found in neurological outcomes (59.0% *vs.* 53.0%, P=0.28) or mortality (20.9% *vs.* 22.8%, P=0.7) between the IIT group (4.4–6.0 mmol/L) and the conventional therapy group (<10 mmol/L); however, a higher incidence of severe hypoglycemia was observed in the IIT group (4.9% *vs.* 0.0%, $P < 0.0001$) during the 2-year follow-up period. Similarly, in another multicenter RCT study of 188 SBI patients,[75] no differences were found in 90-day neurologic outcomes (26.6% *vs.* 31.6%, P=0.4) and 28-day mortality (28.6% *vs.* 28.9%, P=0.9) between the IIT group (4.4–6.0 mmol/L) and the conventional therapy group (5.5–9 mmol/L); however, the incidence of hypoglycemia was significantly higher in the IIT group (51.1% *vs.* 19.3%, $P < 0.001$). Thus, IIT that is used to maintain blood glucose at 4.4–6.0 mmol/L is not recommended.

The appropriate range of blood glucose in SBI patients remains to be determined. A meta-analysis of SBI patients in 2012[76] included 16 RCTs involving 1248 patients and a subgroup analysis of glycemic control goals was performed. Mortality was lower among patients with blood glucose levels of 6.1–10 mmol/L than those receiving ITT, and the neurological

outcomes were better than those receiving less strict glycemic control (<11.1 mmol/L).

Glycemic management of sepsis patients

Question 10: What is the target upper limit for blood glucose among sepsis patients?

Statement 10: The target upper limit for blood glucose among sepsis patients is 10.0–11.1 mmol/L (Grade 2+, weak recommendation).

Rationale: In a sub-study of a prospective observational study, 1045 sepsis patients had at least one blood glucose measurement between 4 h before and >4 h after ICU admission. The first blood glucose measurement in this time window was defined as the glucose level at ICU admission. These levels were ≤3.9 mmol/L in 60 patients (5.7%), normal (3.9–7.8 mmol/L) in 519 patients (49.7%), slightly elevated (7.8–11.0 mmol/L) in 267 patients (25.6%), and significantly elevated (≥11.1 mmol/L) in 199 patients (19.0%). The percentages of diabetic patients with normal, slightly elevated, and significantly elevated glucose upon ICU admission were 10.8%, 21.0%, and 53.3%, respectively. Diabetic or non-diabetic patients with significantly elevated blood glucose (≥11.1 mmol/L) had significantly increased 30-day mortality rates (aHR=1.66, 95% CI: 1.24–2.2).[77] A retrospective study of 1527 patients with community-acquired sepsis showed that increased blood glucose (≥11.1 mmol/L) was associated with increased in-hospital, 30-day, and 90-day mortality, and this association was more stable in diabetic than non-diabetic patients.[78] A prospective, randomized controlled multicenter study assessing the relationship between intensive glucose control and mortality among sepsis patients was prematurely terminated because the hypoglycemia was significantly more prevalent in the intensive treatment group than in the control group.[40] The blood glucose target for the intensive glycemic control group was 5.0–6.1 mmol/L. In the conventional treatment group, insulin pumping was initiated if blood glucose was >11.1 mmol/L and the blood glucose target was 10.0–11.1 mmol/L. Hypoglycemia occurred in 30/247 (12.1%) and 5/241 (2.1%) patients in the treatment and control groups, respectively. There were no significant differences in 28-day fatality, the incidence of acute renal failure, the number of patients requiring renal replacement or vasoconstrictor drugs, or the number of days without a ventilator between the two groups.

NICE-SUGAR is the largest study to date that has assessed the glycemic management of critically ill patients, and 21% of the enrolled subjects had sepsis at the time of randomization. Patients receiving intensive glucose therapy had a similar 90-day fatality rate as those receiving conventional glucose-lowering therapy. In the conventional group, insulin therapy was initiated at blood glucose levels >10.0 mmol/L.[60]

Question 11: What is the target lower limit of blood glucose in sepsis patients?

Statement 11: The target lower limit of blood glucose is 3.9–4.4 mmol/L in sepsis patients (Grade 2+, weak recommendation).

Rationale: A prospective study of 418 sepsis patients from three hospitals in Uganda found that hypoglycemia (<4.4 mmol/L) was an independent risk factor for in-hospital fatality (adjusted hazard ratio[aHR]=1.9, 95% CI: 1.1–3.3)

compared with normoglycemia (4.4–6.1 mmol/L), while hyperglycemia had no impact on mortality risk.[79] A re-analysis of data from a large, multicenter, prospective cohort study found that the 28-day fatality rate in sepsis patients with hypoglycemia (<3.9 mmol/L) upon ICU admission was 35.3% (24/68). This was significantly higher than that found in patients with blood glucose levels of 3.9–7.2 (18.7%, 99/529), 7.2–10.0 (16.5%, 36/218), and ≥10.0 mmol/L (24.6%, 54/301).[80] Thus, it is recommended that the lower limit of blood glucose should be set at 3.9–4.4 mmol/L for sepsis patients.

Glycemic management during severe acute pancreatitis (SAP)

In patients with SAP, extensive necrosis and inflammatory edema occur in the pancreas, and pancreatic endocrine and exocrine cells experience varying degrees of damage which may reduce the absolute number of islet β-cells or the number of functioning islet β-cells, thus aggravating islet β-cell injury and affecting the regulation of glucose homeostasis. SAP is an independent risk factor for hyperglycemia.[81] As the disease progresses, hyperglycemic levels correlate closely with the degree and severity of inflammation,[82,83] and in turn, affect SAP outcomes.[84,85] Therefore, appropriate control of blood glucose levels is essential for the appropriate management of SAP.

Question 12: What are the goals for glycemic management of SAP patients?

Statement 12: The target blood glucose level for SAP patients is 7.8–10.0 mmol/L and insulin therapy is suggested to start from a threshold of ≥10.0 mmol/L (Expert opinion).

Rationale: In recent years, many large-scale multicenter randomized controlled trials have shown that good control of blood glucose can improve the outcomes of critically ill patients.[38,86,87] However, there is still a lack of in-depth research on the glycemic management of SAP patients worldwide. As a result, many researchers have developed a glycemic control protocol for SAP patients that is based on strategies used for other critically ill patients.[88,89] Wu et al.[89] showed that intensive glycemic control (a blood glucose level of 6.1–8.3 mmol/L) reduces blood glucose variability, lowers the risk of infection, and promotes patient recovery. Meanwhile, the glucose lability index (GLI) is positively associated with ICU mortality in SAP patients and has a good predictive value. However, a large, multicenter, randomized study found that in SAP patients, there was no treatment-derived benefit to maintaining a stricter blood glucose level of 4.5–6.1 mmol/L than the target of 7.8–10.0 mmol/L. At the same time, patients with strict glycemic control had higher mortality and a 10–15 fold higher incidence of hypoglycemia.[60] While severe hypoglycemia is not a common concern among pancreatic diabetes patients on insulin treatment,[90] lower target blood glucose levels increase the risk of hypoglycemia.[91] Several RCTs have shown that IIT (3.9–6.1 mmol/L) significantly increases the risk of severe hypoglycemia in critically ill patients.[40,60,73,92–94] Thus, the recommended target blood glucose range for SAP patients is 7.8–10.0 mmol/L, which is highly safe and reduces the risk of hypoglycemia associated with IIT. Since islet β-cell damage affects glycemic regulation and increases the risk of hyperglycemia, glycemic control should be managed similarly in SAP patients as diabetic patients.

Glycemic management in the ICU following major surgery

High blood glucose levels are often present in critically ill patients following major surgery, which is associated with trauma, operation-related outcomes, and stress. Abnormal postoperative blood glucose levels in the ICU increase the incidence of complications and fatality. Thus, strict control of blood glucose levels is required for critically ill patients following major surgery.

Question 13: What is the impact of dysglycemia on postoperative outcomes in non-diabetic critically ill patients following major surgery?

Statement 13: We suggest controlling hyperglycemia while avoiding hypoglycemia and reducing blood glucose variability in non-diabetic critically ill patients following major surgery (Grade 2+, weak recommendation).

Rationale: Hyperglycemia is a common concern after major surgery, especially surgery on the chest and abdomen.[95] Clinical studies[96,97] have shown that postoperative hyperglycemia increases incision infections, retards wound healing, and elevates the incidence of acute kidney injury and cardiovascular and cerebrovascular accidents. Hyperglycemia also correlates closely with mortality, disability, and length of hospital stay. An observational study of critically ill patients undergoing surgery showed significantly higher fatality (OR=4.8, 95% CI: 1.4–20; *P*=0.02) among those with a blood glucose level >7.8 mmol/L than those with a blood glucose level of 4.4–7.8 mmol/L.[98] Another observational study found that patients with postoperative glucose >10.0 mmol/L had a higher incidence of postoperative complications, including acute kidney injury (OR=2.58), arrhythmias (OR=2.40), and sepsis (OR=3.86) than those with glucose <10.0 mmol/L.[99] However, postoperative hypoglycemia is also strongly associated with increased postoperative infection rates, poor wound healing, and fatality.[97,100] An observational study of patients undergoing cardiac surgery found that postoperative hypoglycemia (blood glucose <3.9 mmol/L) significantly increased postoperative fatality (OR=5.47, 95% CI: 3.14–9.5%) and disability (OR=4.66, 95% CI: 3.55–6.1%) rates.[101] Patients with even one episode of hypoglycemia during the perioperative period had a higher risk of death.[102] Of note, large variability in blood glucose is even more harmful than small increases. Blood glucose variations increase postoperative infections, cardiovascular complications, and length of ICU stay.[97,103,104] An observational study[105] suggests that blood glucose variation >6 mmol/L significantly increases the incidence of postoperative atrial fibrillation (16.4% *vs.* 11.6%), and length of ICU stay (63.1 *vs.* 32.7 h) than a glucose variation of 0–2.0 mmol/L, and that high glycemic variability is independently associated with poor postoperative outcomes. Meanwhile, there is a dose-effect relationship between postoperative hyperglycemia, hypoglycemia, high glycemic variability, and poor outcomes after major surgeries.[96,102] While controlling postoperative hyperglycemia is important, therefore, attention should focus on avoiding hypoglycemia and reducing blood glucose variability.

Question 14: How do different levels of glycemic control affect postoperative outcomes after major surgery in non-diabetic patients?

Statement 14: We recommend that blood glucose is maintained at 7.8–10.0 mmol/L in non-diabetic critically ill patients after major surgery (Grade 1+, strong recommendation).

Rationale: In patients undergoing cardiac, major thoracic, and abdominal surgeries, lowering postoperative hyperglycemia with insulin reduces complications and mortality risk.[106,107] However, there is still debate about the optimal range of blood glucose. A RCT study of postoperative patients in the surgical ICU showed that intensive glycemic control (4.4–6.1 mmol/L) resulted in lower short-term postoperative fatality and disability rates than glucose controlled at 10.0–11.1 mmol/L.[38] However, intensive glycemic control significantly increased the risk of hypoglycemia and failed to improve final clinical outcomes.[108,109] According to a systematic review of 27 RCTs,[110] while strict control of blood glucose (4.4–6.1 mmol/L) in postoperative critically ill patients had a similar short-term postoperative fatality rate (risk ratio[RR]=0.99, 95% CI: 0.92–1.0%), 3–6-month fatality rate (RR=1.02, 95% CI: 0.97–1.0%), incidence of sepsis (RR=1.00, 95% CI: 0.89–1.1%), and dialysis rate (RR=0.97, 95% CI: 0.84–1.1%) than less strict glycemic control (7.8–10.0 mmol/L), the incidence of hypoglycemia was approximately fourfold higher after strict control of blood glucose (RR=4.86, 95% CI: 3.16–7.4%). In another systematic review of 15 RCTs, strict glycemic control (4.4–8.3 mmol/L) reduced the overall postoperative infection rate (RR=0.586, 95% CI: 0.504–0.68%), wound infection rate (RR=0.620, 95% CI: 0.422–0.91%), and the length of ICU stay (−0.428 day, 95% CI: −0.833 − −0.022 day), but significantly increased the incidence of postoperative hypoglycemia (RR=3.145, 95% CI: 1.928–5.131) and severe hypoglycemia (RR=3.821, 95% CI: 1.796–8.127). Therefore, relatively strict blood glucose levels of 7.8–10.0 mmol/L balance the efficacy and safety of glycemic management following major surgery.

Glycemic management of severely burned patients

Severe stress is present in burn patients, especially those who are severely burned, which frequently results in stress-induced hyperglycemia. This, in turn, increases the risk of complications and death, indicating that blood glucose should be managed cautiously in severe burn patients. This section describes available data from evidence-based medical studies and expert advice to provide recommendations for the glycemic management of severe burn patients, including target blood glucose, care management, and precautions.

Question 15: How does stress-induced hyperglycemia differ for severe burns patients? Is glycemic intervention required?

Statement 15: We suggest that severe burn patients receive timely blood glucose intervention and that effective measures be taken to control hyperglycemia (Grade 2+, weak recommendation). Severe burn patients should avoid excessive glycemic variability (Grade 1+, strong recommendation).

Rationale: Severe stress reactions usually occur after severe burns, followed by insulin resistance and hypermetabolism, as well as significant and sustained increases in catecholamines, glucocorticoids, and glucagon, that increase blood glucose.[24,111] Jeschke et al.[112] investigated 977 children with severe burns and showed that resting energy expenditure was

significantly higher 6 months, 1 year, and 2 years after burns than over the same time period in control patients ($P < 0.05$). Urine norepinephrine and epinephrine also increased significantly 2 months and 18 months after burns ($P < 0.05$). Wade et al.[113] described metabolic disorders characterized by hypermetabolism, hypercortisolemia, and insulin resistance 6 months and 9 months after burns.

Hyperglycemia after burns is associated with an increased risk of complications such as sepsis, and stress-induced hyperglycemia can increase the risk of mortality in critically ill patients.[26] Ray et al.[114] found that a postburn glucose level >8.3 mmol/L on admission was the only independent predictor of sepsis (area under the curve[AUC]=0.736) and that postburn hyperglycemia was also a predictor of secondary pneumonia and urinary tract infection (AUC=0.766 and 0.802, respectively). Dahagam et al.[115] conducted a retrospective analysis of 462 critically ill patients admitted into burn ICUs over four consecutive years using multivariate regression analysis and showed a significant negative correlation between admission glucose and average glucose with time not requiring mechanical ventilation and length of ICU and hospital stay. Thus, we recommend that patients with severe burns receive timely blood glucose intervention and management and that effective measures should be taken to control hyperglycemia.

Excessive blood glucose variability after burns is an independent risk factor for poor outcomes in burn patients. Excessive blood glucose variability increases the risk of hypoglycemia. Hill et al.[116] showed that 30% of hypoglycemic episodes were caused by excessive blood glucose excursions (hourly excursion >2.8 mmol/L) in burn patients. Pisarchik et al.[53] conducted a retrospective study of 172 non-diabetic patients with secondary and tertiary burns and found that 100% of patients developed sepsis when blood glucose variability (difference between the maximum and minimum daily blood glucose levels) >6 mmol/L and the average glucose level >8 mmol/L. Multivariate analysis showed that increased blood glucose variability was significantly associated with an increased incidence of sepsis and mortality (r=0.61, r=0.7, $P < 0.01$, respectively).

A high frequency of blood glucose variability also affects the outcomes of severe burn patients. Pidcoke et al.[117] found that the incidence of septic shock (58% *vs.* 26%, $P < 0.001$) and mortality (50% *vs.* 22%, P=0.041) was higher in severe burn patients with high glycemic variability (frequency of blood glucose <4.4 or >6.1 mmol/L) than those with low glycemic variability (56% ± 6% *vs.* 43% ± 5%). In another study, 192 critically ill patients were divided into low risk, low to medium risk, medium to high risk, and high-risk groups according to their average daily risk range (ADRR) of blood glucose variability. The mortality of patients gradually increased from 25% in the low-risk group to 60% in the high-risk group (26%, 36%, 44%, and 60% in the four groups, respectively, $P < 0.001$). Post hoc analysis after matching the burn area and wound score indicated that the ADRR was the only blood glucose index significantly associated with the mortality of patients <43 years of age ($P < 0.01$).[118] Dahagam et al.[115] also confirmed that in critically ill patients with severe burns, glycemic variability was higher among those who died than those who survived (26%[23–32] *vs.* 21%,[14–27], $P < 0.05$), and multiple regression analysis showed that high glycemic variability was associated with prolonged hospital stay ($P < 0.05$). Thus, excessive blood glucose variabil-

ity and frequency of blood glucose falling outside the normal range should be avoided.

Question 16: How should target glucose, care guidelines, and precautions be managed in severe burn patients?

Statement 16: We suggest maintaining random blood glucose levels at 6.1–7.8 mmol/L in severe burn patients (Grade 2+, weak recommendation).

Rationale: Considering the intense stress that occurs following severe burns and the increased risk of infection and death resulting from hyperglycemia, glycemic control in severe burn patients should be the same or lower than the target levels of other critically ill patients. Jeschke et al.[119] defined good glycemic control as an average daily blood glucose of 7.8 mmol/L and suggested maintaining blood glucose <7.8 mmol/L during 70% of the hospital stay, a 6 am target glucose of 7.2 mmol/L, and 75% of the blood glucose levels <7.2 mmol/L. In a study of 208 severe burn patients, there was a significant reduction in resting energy expenditure ($P < 0.05$) and inflammatory biomarkers such as IFN-γ, IL-10, IL-7, IL-8, IL-5, IL-6, and monocyte chemotactic protein-1 (MCP-1) ($P < 0.05$) in the group with well-controlled glucose. In addition, blood glucose levels of 7.2 mmol/L at the 6 am measurement and daily average blood glucose levels of 7.8 mmol/L were associated with a lower postburn sepsis incidence and mortality ($P < 0.05$).

Stoecklin et al.[120] assessed whether intensive glycemic control is required for severe burn patients. A retrospective analysis of adult burn patients >15 consecutive years showed significantly more hypoglycemic episodes (2.4–4.0 mmol/L) in those under strict glycemic control (4.0–6.0 mmol/L) than those under moderate glycemic control (6.0–8.0 mmol/L) (76/9964 *vs.* 26/9619, $P < 0.001$). This was especially true for severe hypoglycemic episodes (10/9964 *vs.* 0/9619, P=0.002), suggesting that there is a high risk of hypoglycemia associated with intensive glycemic control in burn patients. Thus, blood glucose should be managed more rigorously in burn patients than in other critically ill patients, and it is recommended that the random blood glucose target is 6.1–7.8 mmol/L.

Glycemic management of drug-induced hyperglycemia

Rational glycemic control requires an assessment of more complex goals and individual patient characteristics such as baseline circumstances and medication use, which can complicate glycemic management.[59,121,122] Since glycemic control of some other medical conditions has been discussed in previous sections, this section only addresses management strategies for drug-induced hyperglycemia, such as that resulting from glucocorticoid use, among critically ill patients.

Question 17: How is blood glucose controlled in patients receiving glucocorticoid treatment?

Statement 17: For inpatients receiving glucocorticoids, less strict blood glucose goals are suggested (Expert opinion).

Rationale: In critical care medicine, glucocorticoids are commonly used for the treatment of conditions such as ARDS and septic shock. They may cause hyperglycemia in both diabetic and non-diabetic patients.[123,124] A meta-analysis of 21 randomized controlled trials of glucocorticoid therapy for adult patients with septic shock showed that the risk of hyperglycemia

was higher in patients receiving glucocorticoids than in controls (RR=1.11, 95% CI: 1.0–1.16).[124] Glucocorticoid-related hyperglycemia treatment must also consider the expected time of onset and duration of hyperglycemia when determining the glucocorticoid regimen. Patients on glucocorticoid therapy should be monitored for blood glucose, and medications such as insulin should be administered to control blood glucose if needed. Glucose-lowering therapy should be adjusted as the glucocorticoid dosage changes. Under glucocorticoid therapy, a less strict target of blood glucose control is recommended.[125]

How can Blood Glucose be Safely Controlled?

Insulin use for the glycemic management of critically ill patients

Preparation of insulin solutions for infusion

Question 18: How should insulin solutions be prepared for infusion?

Statement 18: We suggest preparing insulin solutions for infusion at an insulin concentration of 1 U/mL. The effect of insulin adsorption on treatment can be reduced by priming the tubing with 20 mL insulin solution (Expert opinion).

Rationale: Insulin solutions for infusion should be prepared at standard concentrations, and a synthetic human insulin solution of 1 U/mL is recommended in most protocols. Insulin may be added to 0.9% sodium chloride solution, Ringer lactate solution for injection, Ringer solution for injection, or a 5% glucose solution. Glass or plastic containers (polyvinyl chloride [PVC], ethylene-vinyl acetate, polyethylene, or other polyolefin plastics) may be used to prepare insulin solutions for infusion. Insulin dissolved in 0.9% sodium chloride solution in a PVC container keeps stable for 168 h at 2–8°C.[126] Insulin can be adsorbed onto the tubing used for intravenous infusion, and the degree of adsorption is influenced by temperature, insulin concentration, and the injection rate. The use of a 20 mL insulin solution to prime the tubing reduces the loss of insulin resulting from adsorption.[127] A randomized controlled study found that even experienced critical care nurses delay treatments and make mistakes in preparing medications.[128] While some countries have commercially available insulin solutions for infusion, such as Myxredlin, no products are currently available in China. Since the insulin solution for injection is a high-risk drug, we recommend that insulin solutions for infusion should be prepared at the preparation center of hospitals to prevent adverse events resulting from incorrect insulin concentrations or contamination.

Transitional regimens for insulin use

Question 19: What are the best transitional regimens for insulin use?

Recommendation 19: We suggest that critically ill patients transition to subcutaneous administration of insulin after stopping intravenous infusion of insulin to maintain glycemic stability (Expert opinion).

Rationale: Transitioning to a subcutaneous injection regimen can reduce rebound hyperglycemia after continuous insulin infusion has concluded.[129] There are several regimens for transitioning from an intravenous insulin infusion to subcutaneous insulin therapy, including long-acting insulin (e.g.,

insulin glargine) injected every 24 h or intermediate-acting insulin (e.g., neutral protamine zinc insulin) injected every 6–12 h. It is recommended that the initial dosage of subcutaneous insulin should be administered at least 2–4 h before stopping insulin infusion to prevent hyperglycemia. The total daily insulin (TDI) dosage infused intravenously can be used as a reference for determining the subcutaneous insulin dosage in critically ill patients. As a result of insulin loss resulting from adsorption onto the container and tubing, the initial subcutaneous insulin dosage can be reduced to 60–80% of the TDI, which has been validated in clinical studies of cardiac surgery and critically ill patients.[129,130] Concurrent changes to other medical or nutritional regimens must be considered when implementing the transitional regimen of insulin use. A real-world study found a reduction in hypoglycemia and an increase in hyperglycemia following the transition to subcutaneous administration of insulin.[131] Transitional regimens of insulin use should be individualized and refined to avoid large variations in blood glucose among critically ill patients.

Overview and prevention of insulin-related adverse events

Insulin therapy is an important way to control hyperglycemia. When the disease is chronic, insulin therapy may be the most important glycemic control measure.[132] Insulin has been used for nearly 100 years in clinical practice, and insulin-related adverse events are very rare.[133] The major concern with insulin use is hypoglycemia and other adverse events such as allergy and local skin reactions are infrequent with the wide use of highly purified animal and human insulin. Common adverse reactions are described in Table 2.

Use of hypoglycemic drugs for the glycemic management of critically ill patients

Hyperglycemia and insulin resistance are common among critically ill patients.[137] Insulin resistance refers to a decrease in the efficiency of glucose uptake and utilization of insulin for various causes, which leads to the excessive secretion of insulin required to maintain blood glucose stability. To overcome insulin resistance, clinicians often increase the insulin dosage used, which may result in hypoglycemia, hypokalemia, hypomagnesemia, and other complications.[138]

Question 20: How should blood glucose be controlled in the event of insulin resistance in critically ill patients?

Statement 20: When critically ill patients develop insulin resistance, metformin is suggested in combination with insulin (Grade 2+, weak recommendation).

Rationale: Metformin is known as an "insulin sensitizer." In a randomized, double-blind clinical trial conducted at the Mazandaran Heart Center, 100 patients with type 2 diabetes admitted to the ICU after cardiac bypass surgery (CABG) were randomized to a group receiving conventional insulin or insulin plus metformin. Significantly lower average glucose levels were found among patients in the insulin plus metformin group than those in the conventional insulin group ($P < 0.05$).[139] In a randomized controlled study, patients with a systemic inflammatory response (SIRS) were randomly assigned to a group receiving insulin therapy (IIT) or insulin plus metformin (IIT + MET). IIT + MET treatment reduced the need for insulin ($P < 0.05$),

Table 2
Insulin-related adverse events.

Common adverse events	Clinical manifestations	Prophylaxis
Hypoglycemia	See "Hypoglycemia" section for details.	
Allergy	Induration, erythema, nausea, diarrhea, urticaria, angioedema, rash, dyspnea, and even shock.	Use of hypoimmunogenic insulin
Lipoatrophy	Lipoatrophy is characterized by depressed skin around the injection site[133].	Use of high-purity insulin
Fat hypertrophy	Soft subcutaneous nodules at frequently injected sites.	Frequent change of injection sites
Insulin resistance	Decreased insulin sensitivity[134].	
Refractive abnormality	Blurred vision; a rapid drop in blood glucose influences the osmotic pressure of the lens and vitreous body and makes the water in the lens escape, leading to decreased refractive index and hyperopia. Refractive abnormality usually resolves in a few weeks.	
Insulin-induced edema	Commonly seen in patients with rapid glycemic control following insulin use and is generally self-resolving[135].	
Weight gain	Associated with insulin-enhanced anabolism and increased appetite following a decrease in blood glucose.	
Others	Other rare adverse events including nausea, vomiting, leukocytoclastic vasculitis, local amyloidosis, and even death have been reported[136].	

lowered the insulin and C peptide levels ($P < 0.05$), and decreased the levels of tumor necrosis factor-α and IL-6 ($P < 0.05$) without causing hyperlactatemia or acidosis.[138] Thus, treatment with metformin in combination with insulin is safe and effective in the event of insulin resistance.

Glucagon-like peptide 1(GLP-1) is an endogenous incretin that enhances glucose-dependent insulin secretion, an effect that disappears as glucose concentrations normalize.[140] GLP-1 is shown to significantly reduce plasma glucose, hemoglobin A1c, fructosamine, and free fatty acid concentrations and improves insulin sensitivity and β-cell function in patients with type 2 diabetes.[141]

Principles of nutritional treatment of patients with severe hyperglycemia

Question 21: What are the nutritional therapeutic options for hyperglycemia in critically ill patients?

Statement 21: Enteral nutrition is suggested for critically ill patients with hyperglycemia, and diabetes-specific formulas are preferred (Grade 2+, weak recommendation).

Rationale: Enteral nutrition influences glycemic control. A meta-analysis of six RCTs involving 265 non-diabetic patients with acute pancreatitis showed that the incidence of hyperglycemia and the need for insulin were lower following enteral than parenteral nutrition support.[142] Thus, enteral nutrition is recommended for critically ill patients with good intestinal tolerability.[3,4,143]

Diabetes-specific formulas (DSFs) help to control blood glucose by slowing down carbohydrate absorption and decreasing the total amount absorbed, thus reducing peak blood glucose levels after feeding.[143,144] In modified carbohydrate formulas, sustained-release starch is used, and fructose and dietary fiber content are increased,[143] making it easier to control hyperglycemia and maintain glycemic stability. Multiple studies indicate that DSFs using modified carbohydrates improve glycemic control in patients. In a prospective RCT of 41 critically ill patients with hyperglycemia, low-carbohydrate formulas reduced blood glucose levels, insulin use, and glycemic variability among enterally fed, critically ill patients with hyperglycemia.[145] In a prospective multicenter RCT of 157 mechanically ventilated, critically ill patients with hyperglycemia, insulin use was significantly lower and glycemic control higher among patients treated with DSFs than those receiving the standard formulas.[146] Another prospective RCT of 104 critically ill patients with severe acute ischemic stroke showed that DSFs improved glycemic control and insulin sensitivity.[147] A meta-analysis of 23 studies with 784 patients concluded that the average postprandial glucose decreased by 1.03 mmol/L among patients receiving DSFs than those receiving standard formulas.[148] A meta-analysis also suggested that higher levels of monounsaturated fatty acids may improve blood pressure and glycolipid metabolism in diabetes patients.[149]

Question 22: What is the rate of glucose infusion among critically ill patients with hyperglycemia during nutritional therapy?

Statement 22: When using parenteral nutrition for critically ill patients with hyperglycemia, experts suggest that the rate of glucose infusion should not exceed 5 mg/kg/min (Expert opinion).

Rationale: When stress-induced hyperglycemia occurs during a critical illness or following a major surgical procedure, the glucose infusion rate has a great impact on blood glucose levels during parenteral nutrition (PN) therapy. According to the 2019 ESPEN guidelines for clinical nutrition in the ICU, it is recommended that the total amount of carbohydrates should not exceed 5 mg/kg/min during PN treatment of critically ill patients.[3] This recommendation is largely based on a physiological understanding. A RCT in patients from surgical ICUs showed that an increased energy supply of intravenous glucose did not inhibit endogenous glucose production and net protein loss but was associated with hyperglycemia and a higher demand for insulin.[150] The tolerance of critically ill patients for glucose infusion was lower than it was for other patients. A study of critically ill burn patients found that glucose oxidation reached a steady state when glucose was infused at 5 mg/kg/min.[151] In a retrospective study of 102 non-diabetic adult patients receiving parenteral nutrition, 49% of patients experienced hyperglycemia when the glucose infusion rate was >5 mg/kg/min, 11% experienced hyperglycemia when the glucose infusion rate was 4.1–5.0 mg/kg/min, and no hyperglycemia was recorded when the glucose infusion rate remained at ≤4 mg/kg/min.[152]

Parenteral nutrition (PN)

Question 23: How should insulin be formulated in parenteral nutrition for critically ill patients?

Statement 23: Intravenous insulin alone is suggested for controlling hyperglycemia during PN therapy of critically ill patients (Expert opinion).

Rationale: PN can cause hyperglycemia that requires insulin therapy. Insulin administration modes include intravenous infusion, subcutaneous injection, and direct addition to PN.

A retrospective study of 122 patients observed the effect of intravenous insulin infusion and subcutaneous insulin injection on blood glucose in critically ill patients. The incidence of PN-associated hyperglycemia was also compared between the two modes of insulin administration. The time to target blood glucose was lower following intravenous infusion than subcutaneous injection (62% *vs.* 43%, *P*=0.008), indicating that intravenous insulin infusion improves glycemic control among critically ill patients.[153]

McCulloch et al.[154] proposed that rational glycemic control can be achieved by adding insulin to PN in the short term;[155,156] however, the subjects included in this study were not in serious condition and there is no evidence that insulin can be added to PN in critically ill patients. Two small studies showed that lipid emulsions, trace elements, and multivitamins contained in PN can affect insulin efficacy.[157–159] In clinical practice, optimal and safe insulin containing PN formulas cannot be provided because of a lack of well-trained pharmacists. The addition of insulin to PN formulas at the bedside may increase the incidence of infection because no rigid aseptic measures are taken.[158] There is also an increased risk of pellet precipitation. Thus, this method is not widely recommended for the treatment of critically ill patients. In summary, we recommend that the addition of insulin to PN formulas should be avoided for use in critically ill patients, and in regions with fewer resources. In critically ill patients with PN, intravenous insulin alone is recommended to control blood glucose.

Monitoring and Control of Hypoglycemia in Critically Ill Patients

Early identification of hypoglycemic episodes in critically ill patients

Question 24: How should hypoglycemic episodes be identified early in critically ill patients?

Statement 24: The possibility of hypoglycemia should be considered when there are symptoms such as increased heart rate, decreased blood pressure, widened pulse pressure, and sweating that cannot be explained by other causes in critically ill patients with impaired consciousness or on mechanical ventilation under analgesia and sedation. Blood glucose testing should be performed immediately to confirm the diagnosis (Expert opinion).

Rationale: Despite significant clinical signs of hypoglycemia, hypoglycemic symptoms may be less specific in critically ill patients because of sympathetic activation resulting from severe underlying diseases, trauma, infection, stress, and potential central nervous system damage.[160] Especially in patients with impaired consciousness (e.g., craniocerebral injury, delirium, and Alzheimer's disease) or on mechanical ventilation under sedation, the absence of patient complaints further obscures the symptoms of hypoglycemia. One study found that up to 59.18% of critically ill patients with hypoglycemia were on mechanical ventilation.[21] Even in the absence of specific clinical signs, the possibility of hypoglycemia should be considered as early as possible in the event of epinephrine-like reactions and/or symptoms of central nervous system insufficiency in critically ill patients. This is especially critical if the patient presents with symptoms such as increased heart rate, decreased blood pressure, widened pulse pressure, sweating, or altered consciousness that cannot be explained by other causes. An early and definitive diagnosis should be made immediately by measuring blood glucose levels.

Hypoglycemia treatment strategies in critically ill patients

Question 25: How should blood glucose levels be monitored in critically ill patients who have experienced hypoglycemia?

Statement 25: In critically ill patients at high risk for hypoglycemia, blood glucose levels should be monitored every 1–2 h, while in critically ill patients with hypoglycemia, blood glucose should be monitored within 15 min after glucose therapy until blood glucose stabilizes within the target range (Grade 2+, weak recommendation).

Rationale: The most common cause of hypoglycemia, especially severe hypoglycemia, is a delay in measurement.[42] Given that many protocols require that blood glucose should be monitored every 4 h, there is a >10% incidence of hypoglycemia among critically ill patients.[40,41] Thus, monitoring critically ill patients at high risk for hypoglycemia at this frequency is not recommended. High-risk patients who are receiving intravenous insulin infusion should be monitored every 1–2 h to quickly identify blood glucose levels that are outside the target range. A retrospective analysis of 6069 insulin infusion related events in 4588 critically ill patients showed that hypoglycemia can progress to severe hypoglycemia within 12 min after onset;[42] thus, more frequent blood glucose monitoring is warranted. We recommend re-checking blood glucose levels within 15 min after glucose infusion in hypoglycemia patients and repeating the testing until blood glucose levels stabilize within the target range. Importantly, the duration of hypoglycemia may vary in critically ill patients receiving exogenous insulin therapy. For instance, renal failure prolongs the half-life of insulin, leading to insulin accumulation and extending the duration of hypoglycemia.

Question 26: How should hypoglycemia be treated?

Statement 26: In patients with hypoglycemia during insulin use, insulin infusion should be stopped immediately and 15–20 g glucose administered intravenously to avoid nervous system damage. Glucose should be further administered until blood glucose levels are within the target range. Meanwhile, iatrogenic hyperglycemia should be avoided (Grade 2+, weak recommendation).

Rationale: For severe hypoglycemia, interruption of insulin infusion is the first step in treatment. However, interrupting the insulin infusion alone may not be sufficient, and additional treatment with intravenous glucose infusion is usually required. Meanwhile, iatrogenic hyperglycemia should be avoided. In some reports, a formula is used to calculate a patient's glucose dosage: 50% glucose dosage (g)=[100 − glucose value (mg/dL)] × 0.2 g. It was found that 10–20 g glucose could increase blood glucose to 4.4–6.1 mmol/L within 30 min in 97.5% of hypoglycemic patients receiving intravenous insulin

infusion.[42] We suggest that 15–20 g glucose be intravenously infused to reduce the incidence of blood glucose levels occurring outside the target range. There are no clinical studies assessing the effect of infusions of different glucose concentrations on the body. As a result of the high osmolality of 50% glucose, caution should be exercised when administering such a high concentration of glucose intravenously. Infusion of a large volume of 10% or 25% glucose over a short period of time can increase the third space burden and worsen tissue edema in patients with heart failure or in infected patients with increased tissue permeability. Given the existing clinical evidence, the physiological effects of different glucose concentrations used for hypoglycemia treatment require further studies.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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