MÍNIMO INDISPENSABLE PARA EL PROGRAMA DE ESTUDIOS

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GLYCEMIC CONTROL AND INTENSIVE INSULIN THERAPY IN CRITICAL ILLNESS

INTRODUCTION — Hyperglycemia associated with critical illness (also called stress hyperglycemia or stress diabetes) is a consequence of many factors, including increased cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis [1]. Insulin resistance may also be a contributing factor, since it has been demonstrated in more than 80 percent of critically ill patients [2].

Hyperglycemia was previously considered an adaptive response essential for survival and was not routinely controlled in intensive care units (ICU) [3,4]. However, uncontrolled hyperglycemia is associated with poor outcomes has prompted efforts to routinely correct and prevent hyperglycemia in critically ill patients.

Glycemic control in critically ill patients is discussed in this topic review. Nutritional support in critically ill patients is described separately. (See "Nutrition support in critically ill patients: An overview".)

EFFECTS OF HYPERGLYCEMIA — There is a wealth of observational evidence from different patient populations demonstrating that hyperglycemia is associated with poor clinical outcomes in critically ill patients. However, this evidence does not prove that hyperglycemia causes poor clinical outcomes, since hyperglycemia may merely be a marker of severe illness.

Trauma — Patients who are hyperglycemic following trauma have an increased mortality rate, hospital length of stay, ICU length of stay, and incidence of nosocomial infection [5-8]. This was illustrated by a prospective cohort study of 1003 patients who were admitted to an ICU following trauma [7]. Hyperglycemia (blood glucose ≥200 mg/dL [12.2 mmol/L]) was present in 255 patients (25 percent) at the time of ICU admission. Compared to normoglycemic patients, hyperglycemic patients

had a significantly increased mortality rate (26 versus 12 percent) and incidence of nosocomial infection (52 versus 32 percent).

Hyperglycemia is also associated with worse neurologic outcomes and increased intracranial pressure in patients with traumatic brain injury [9,10]. In a retrospective cohort study of 77 patients with severe traumatic brain injury, hyperglycemia (blood glucose ≥170 mg/dL [9.4 mmol/L]) at the time of ICU admission was an independent predictor of a poor Glasgow coma score five days later [10].

The association between hyperglycemia and adverse outcomes in trauma patients exists regardless of whether the hyperglycemia is present only at ICU admission or persists throughout the ICU stay [8,10]. One prospective cohort study of 942 trauma patients admitted to an ICU found that patients whose blood glucose was elevated at ICU admission (blood glucose ≥200 mg/dL [11.1 mmol/L]), increased during the ICU stay, or was highly variable during the ICU stay had an increased mortality rate, duration of mechanical ventilation, and ICU and hospital length of stay, compared to patients with alternative patterns of glucose control [8].

Medical/surgical — Critically ill medical and surgical patients who are hyperglycemic have a higher mortality rate than patients who are normoglycemic [11-13]. This was illustrated by a retrospective cohort study of 1826 medical and surgical ICU patients [11]:

●Compared to patients who survived, those who died had significantly higher admission blood glucose levels (175 versus 151 mg/dL [9.7 versus 8.4 mmol/L]), mean blood glucose levels (172 versus 138 mg/dL [9.5 versus 7.7 mmol/L]), and maximum blood glucose levels (258 versus 177 mg/dL [14.3 versus 9.8 mmol/L]).

●There was a graded effect, with higher mortality among patients who had higher blood glucose levels. Mortality ranged from 10 percent in patients with a mean blood glucose between 80 and 99 mg/dL (4.4 and 5.5 mmol/L) to 43 percent in patients with a mean blood glucose greater than 300 mg/dL (16.6 mmol/L).

Hyperglycemia is also associated with worse outcomes in several subgroups of critically ill medical patients, including patients with stroke or acute myocardial infarction. Hyperglycemia and glycemic control in these subgroups are discussed separately. (See "Initial assessment and management of acute stroke" and "Glycemic control for acute myocardial infarction in patients with and without diabetes mellitus".)

GLYCEMIC CONTROL — Most clinicians accept that prevention of uncontrolled hyperglycemia is a desirable intervention. However, the optimal blood glucose range is controversial [14]. Numerous clinical trials have compared different ranges of blood glucose in various populations of critically ill patients, some of which are described in this section. Their impact on patient care is described in the next section. (See 'General approach' below.)

Surgical patients

Adults — Trials in surgical patients have reported mixed outcome from intensive insulin therapy (IIT). While one trial initially reported improved mortality (the Leuven surgical trial) associated with IIT, a subsequent trial (Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation [NICE-SUGAR] trial) reported increased mortality in its surgical subgroup. In all trials, patients who received IIT had a significantly increased risk of severe hypoglycemia. Our suggested approach to the management of these patients is presented below. (See 'General approach' below.)

A single center trial (the Leuven surgical trial) randomly assigned 1548 surgical ICU patients to receive IIT or conventional blood glucose management [15]. IIT was defined as an insulin infusion targeting a blood glucose of 80 to 110 mg/dL (4.4 to 6.1 mmol/L). Conventional blood glucose management targeted a blood glucose of 180 to 200 mg/dL (10 to 11.1 mmol/L) and used an insulin infusion only if the blood glucose was greater than 215 mg/dL (11.9 mmol/L). Patients in both arms of the trial were given 200 to 300 grams of intravenous glucose during the first day of ICU admission. In the majority of patients, parenteral nutrition was added to enteral nutrition on the second day of ICU admission if necessary to achieve the caloric goal.

Most patients were adult (mean age 63 years) males (71 percent) who had undergone cardiac surgery (63 percent) and were not severely ill (mean Acute Physiologic and Chronic Health Evaluation [APACHE II] score was 9). The following outcomes were detected:

●The mean blood glucose was significantly lower in the IIT group (103 versus 153 mg/dL [5.7 versus 8.5 mmol/L]).

●ICU mortality was significantly lower in the IIT group (4.6 versus 8 percent). The magnitude of the benefit was greatest among patients who were in the ICU for five days or longer.

●Hospital mortality was significantly lower in the IIT group (7.2 versus 10.9 percent).

●IIT decreased critical illness polymyoneuropathy, acute renal failure, transfusion requirement, and blood stream infections.

●Hypoglycemia (blood glucose <40 mg/dL [2.2 mmol/L]) was more frequent in the IIT group (5.1 versus 0.8 percent).

A concern about this trial was the high mortality rates in the control group; specifically, ICU mortality was 8 percent and hospital mortality was 11 percent. These mortality rates are higher than the 1.5 to 3.5 percent reported for most patients undergoing routine cardiac surgery [16,17]. This high mortality raises the possibility that there was a harmful intervention in the control group that was ameliorated by IIT. One possibility is that the large glucose load administered on the first and second ICU day was harmful to the control group, but not the IIT group, because the IIT group was rescued by its more aggressive insulin regimen.

These findings were supported by a meta-analysis of five randomized trials (1972 patients) that compared IIT to less stringent glycemic control in surgical ICU patients [18]. IIT was defined as a target blood glucose level ≤150 mg/dL (8.3 mmol/L). Patients who received IIT had significantly lower mortality than those who received less stringent glycemic control (7.4 versus 11.8 percent, relative risk 0.63, 95% CI 0.44-0.91). However, the results of the meta-analysis were largely driven by the Leuven surgical trial, an important limitation.

In contrast, when the NICE-SUGAR trial analyzed its surgical patients, there was increased mortality among those who received IIT compared to those who received conventional glucose control [19]. These findings are described in detail below. (See 'NICE-SUGAR trial' below.)

Medical patients — Several trials of tight glucose control in medical patients have reported no mortality benefit and a significant increased frequency of hypoglycemia. Our suggested approach to the management of these patients is presented below. (See 'General approach' below.)

The same investigators who performed the Leuven surgical trial conducted a similar trial exclusively in critically ill medical patients. The single center trial (the Leuven medical trial) randomly assigned 1200 medical ICU patients to receive IIT (target blood glucose level of 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) or conventional glucose control (target blood glucose of 180 to 200 mg/dL [10 to 11.1 mmol/L]) [25]. The insulin infusion protocols and nutritional strategies were the same as the Leuven surgical trial (see 'Surgical patients' above):

●Mean blood glucose was lower in the IIT group than the conventional therapy group (105 versus 160 mg/dL [5.8 versus 8.9 mmol/L])

●IIT did not change overall hospital mortality (37.3 versus 40 percent in the control group)

●IIT significantly reduced ICU length of stay, hospital length of stay, duration of mechanical ventilation, and acute kidney failure

●Hypoglycemia was significantly more common in the IIT group (18.7 versus 3.1 percent)

Like the Leuven surgical trial, the nutritional approach in the Leuven medical trial (ie, glucose loading by adding early total parenteral nutrition to enteral nutrition) is not the standard of care worldwide [26,27]. As a result, the results of this trial are not generalizable to patients who receive a more usual nutritional approach, such as enteral nutrition started early and increased over the first few ICU days.

A more recent trial supports the notion that strict blood glucose control is not beneficial in medical patients. The Corticosteroids and Intensive Insulin Therapy for Septic Shock (COIITSS) trial randomly assigned 509 patients with septic shock who were receiving corticosteroids to either intensive insulin therapy using the same protocol as the Leuven medical trial or conventional blood glucose control [28]. For the latter group, the blood glucose target, insulin dose, and route of administration were left to the discretion of the clinician, although they were encouraged to target a blood glucose level <150 mg/dL (8.3 mmol/L). The trial found no difference in mortality, ICU length of stay, ventilator-free days, or vasopressor-free days.

Mixed patients — Several randomized trials have evaluated IIT in mixed populations of critically ill medical and surgical patients [19,29-34]. At least two of the trials were stopped early for safety. Most trials have reported no mortality benefit. In addition, severe hypoglycemia due to tight glucose control strategies was also associated with increased mortality in some of the trials (NICE-SUGAR). Meta-analyses have been performed in an effort to consolidate the data from numerous randomized trials [18,35-37]. One such meta-analysis of 15 randomized trials (10,140 patients) compared IIT (defined as a target blood glucose level ≤150 mg/dL [8.3 mmol/L]) to less stringent glycemic control in mixed medical and surgical ICU patients [18]. Patients who received IIT had a similar mortality to those who received less stringent glycemic control (26.7 versus 25.6 percent).

Our suggested approach to the management of these patients is presented below. (See 'General approach' below.)

NICE-SUGAR trial — The largest trial was the multicenter Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, which randomly assigned 6104 medical and surgical ICU patients to either IIT (target blood glucose level of 81 to 108 mg/dL [4.5 to 6 mmol/L]) or conventional glucose control (target blood glucose of <180 mg/dL [<10 mmol/L]) [19]. Although the conventional glucose control group was defined only by a maximal blood glucose target, the insulin infusion was reduced and then discontinued if the blood glucose level dropped below 144 mg/dL (8 mmol/L). Compared to the conventional glucose control group:

●The IIT group had a significantly lower time-weighted blood glucose (115 versus 144 mg/dL [6.2 versus 7.9 mmol/L])

●The IIT group had a significantly higher 90 day mortality (27.5 versus 24.9 percent, odds ratio 1.14, 95% CI 1.02-1.28)

●The IIT group had a significantly higher incidence of severe hypoglycemia (6.8 versus 0.5 percent), defined as a blood glucose <40 mg/dL

In the subgroup of 2232 operative patients, those who received IIT had a significantly higher mortality than those who received conventional glycemic control (24.4 versus 19.8 percent, odds ratio 1.31, 95% CI 1.07-1.61).

As an extension of this study, the long term (24 month) neurologic and mortality outcomes of patients with traumatic brain injury (TBI) who participated in the NICE-SUGAR trial have been reported [38]. Data were available in 315 patients (166 patients ITT and 149 conventional therapy). No differences in favorable neurologic outcome (60 versus 53 percent) or mortality (21 versus 23 percent) were reported, despite the higher incidence of severe hypoglycemia with ITT.

VISEP trial — The Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial was a multicenter two-by-two factorial trial conducted in medical and surgical ICU patients with severe sepsis [29]. It compared IIT (target blood glucose level of 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) to conventional glucose control (target blood glucose level of 180 to 200 mg/dL [10 to 11.1 mmol/L]), as well as comparing two methods of volume resuscitation. The IIT arm of the trial was stopped after 488 patients were enrolled because IIT significantly increased the rate of hypoglycemia (12.1 versus 2.1 percent) and serious adverse events (10.9 versus 5.2 percent). The trial then continued with only patients in the conventional therapy group until 537 patients were enrolled. The following outcomes were detected when IIT was compared to conventional glucose control:

●Mean morning blood glucose was significantly lower in the IIT group (112 versus 151 mg/dL [6.2 versus 8.4 mmol/L])

●Hypoglycemia (blood glucose ≤40 mg/dL [2.2 mmol/L]) was significantly more common in the IIT group (17 versus 4.1 percent)

●There was no significant difference in 28 day mortality (24.7 versus 26 percent in the conventional glucose control group), morbidity, or organ failures

●There was a nonstatistically significant increase in 90 day mortality in the IIT group (39.7 versus 35.4 percent)

Glucontrol trial — The Glucontrol trial was a multicenter trial that randomly assigned 1101 critically ill medical and surgical patients to IIT (target blood glucose of 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) or conventional glucose control (target blood glucose of 140 to 180 mg/dL [7.8 to 10 mmol/L]) [30]. The trial was terminated early because of a high rate of unintended protocol violations. IIT significantly increased the rate of hypoglycemia (8.7 versus 2.7 percent). There was no difference in ICU mortality, although the IIT group had a nonsignificant trend toward increased 28 day mortality and hospital mortality.

Children — The effect of IIT was examined in a trial (CHiP) that randomized 1369 children from 16 pediatric ICUs to tight or conventional glycemic control (ie, blood glucose 72 to 126 mg per deciliter [4 to 7 mmol/L] versus 180 to 216 mg per deciliter [10 to 12 mmol/L]) [23]. All participants were children (4 months to 16 years), the majority of whom (60 percent) had cardiac surgery. An insulin-adjusted algorithm was used to achieve targeted blood glucose levels. At 30 days, tight glucose control did not affect mortality and number of ventilator-free days, measured as a composite outcome (mean difference 0.36 days alive and free of mechanical ventilation). Pre-specified subgroup analysis did not identify any patient group (cardiac or non-cardiac) that might gain a mortality benefit from tight glycemic control. Compared to conventional glycemic control, severe hypoglycemia (blood glucose <36 mg per deciliter [2 mmol/L]) occurred more frequently in the tight-glycemic-control group (7 versus 2 percent). Compared to patients without hypoglycemia, patients with at least one episode of hypoglycemia had increased mortality (11 versus 4 percent), an effect which was most pronounced in those who had undergone cardiac surgery (11 versus 2 percent). The achieved target glucose levels (mean over 10 days) were 107 and 114 mg/dL [5.9 and 6.3 mmol/L] in the tight and conventional glycemic control groups, respectively. The lower than expected mean glucose level in the conventional group may have limited the overall analysis.

The HALF-Pint trial (similarly designed to SPECS), compared high and low blood glucose target levels in 713 hyperglycemic critically-ill children (2 weeks to 17 years with two blood glucose levels >150 mg/dL [8.3 mmol/L mmol/L] before intervention). Patients who had undergone cardiac surgery were excluded. The number of ICU-free days was no different among those with a lower target blood glucose level of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) compared with a higher target level of 150 to 180 mg/dL (8.3 to 10 mmol/L) [39]. Also reported in the lower target group were higher rates of hypoglycemia (5 versus 2 percent) and healthcare-associated infections (3 versus 1 percent), but mortality, severity of organ dysfunction, and number of ventilator-free days were no different. Noteworthy, is that patients in the higher target group had a lower than expected mean blood glucose level (123 mg/dL [6.8 mmol/L]), which may have limited the analysis. This trial was stopped early on the basis of low likelihood of benefit and possibility of harm.

A meta-analysis of five randomized trials comprising 3933 patients has confirmed that mortality is unaffected by tight glycemic control in critically ill children [40].

Summary — In mixed adult populations of critically ill medical and surgical patients, IIT (target blood glucose of 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) increased the incidence of severe hypoglycemia and either increased mortality or had no effect on mortality, when compared to the more permissive blood glucose ranges of 140 to 180 mg/dL (7.8 to 10 mmol/L) and 180 to 200 mg/dL (10 to 11.1 mmol/L). Similar trends have been noted in children.

Hypoglycemia — Hypoglycemia is the most common adverse effect of IIT. It occurs in up to 19 percent of patients when defined as a blood glucose <40 mg/dL (2.2 mmol/L) [25], or up to 32 percent of patients when defined as a blood glucose <60 mg/dL (3.3 mmol/L) [41]. Its frequent occurrence is problematic because hypoglycemia can lead to seizures, brain damage, depression, and cardiac arrhythmias [30,42-44]. Hypoglycemia is also a risk factor for death [13,30,43,45]:

●In a post hoc analysis of 6026 patients from the NICE-SUGAR trial described above, patients with moderate or severe hypoglycemia (blood glucose, 41 to 70 mg per deciliter [2.3 to 3.9 mmol per liter] and ≤40 mg per deciliter [2.2 mmol per liter], respectively) had a higher risk of death compared with those without hypoglycemia (adjusted hazard ratio 1.41 [95% CI, 1.21-1.62] and 2.1 [95% CI, 1.59-2.77], respectively) [46].

●As part of a retrospective cohort study of more than 5000 medical and surgical critically ill patients, a nested case-control study found that a blood glucose <40 mg/dL (2.2 mmol/L) was an independent risk factor for death after adjustment for severity of illness, age, mechanical ventilation, renal failure, sepsis, and diabetes (adjusted odds ratio 2.28, 95% CI, 1.41-3.70) [43].

●In the control group of the Glucontrol trial, mortality among patients who had an episode of hypoglycemia was 53.8 percent, compared to only 15.2 percent among patients who had not had an episode of hypoglycemia [30].

In contrast, the Leuven trials found that hypoglycemia did not cause early deaths or neurologic sequelae [47]. This has led some clinicians to believe that transient hypoglycemia may not be harmful [48]. We believe, however, that the preponderance of evidence indicates that iatrogenic hypoglycemia is a life-threatening condition.

The optimal management strategy for insulin-induced hypoglycemia is unknown. However, one retrospective analysis of 105 patients reported that the implementation of a hypoglycemia protocol led to reduced glucose variability compared to a standardized approach [49]. Larger randomized trials demonstrating a mortality benefit are required before hypoglycemia protocols can be routinely used for the management of hypoglycemia in the ICU.

GENERAL APPROACH — We recommend a blood glucose target of 140 to 180 mg/dL (7.7 to 10 mmol/L) in most critically ill adult patients, rather than a more stringent target (eg, 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) or a more liberal target (eg, 180 to 200 mg/dL [10 to 11.1 mmol/L]). This range avoids marked hyperglycemia, while minimizing the risk of both iatrogenic hypoglycemia and other harms associated with a lower blood glucose target. The following evidence supports our approach:

●Hyperglycemia, defined as a blood glucose level greater than 180 to 200 mg/dL (10 to 11.1 mmol/L), is associated with poor clinical outcomes. (See 'Effects of hyperglycemia' above.)

●Stringent intensive insulin therapy regimens (IIT) that target blood glucose range of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) significantly increase the incidence of severe hypoglycemia and may increase mortality, especially when compared with less stringent regimens (eg, target blood glucose range of 140 to 180 mg/dL [7.8 to 10 mmol/L]). (See 'Glycemic control' above and 'Hypoglycemia' above.)

●Patients managed with our blood glucose target had a significantly lower mortality and incidence of hypoglycemia in the largest trial that directly compared our recommended blood glucose target to IIT. (See 'NICE-SUGAR trial' above.)

To achieve the target blood glucose range in adult patients, we first attempt to avoid or minimize the use of intravenous fluids (IVFs) that contain glucose and administer insulin only when necessary [26,27]. The same basic principles apply in pediatric patients with the exception that children (particularly young children) generally require dextrose in maintenance IVF to ensure adequate glucose delivery to avoid hypoglycemia and provide nutrition. Other sources of glucose (eg, IV medications) should be limited in critically ill children. (See "Maintenance intravenous fluid therapy in children", section on 'Dextrose'.)

There is no universally accepted insulin regimen for glycemic control in critically ill patients. However, to avoid prolonged hypoglycemia, which may be harmful in this population, insulin infusions and intermittent short-acting insulin are typically used [50]. Careful monitoring of blood glucose is mandatory to achieve the target range and avoid hypoglycemia. Once the acute illness has resolved, transitioning to longer-acting insulin in the ICU has been shown to be safe in patients who are being enterally fed [51]. Management of insulin infusions and recommendations for transitioning to longer-acting formulations in hospitalized patients is discussed separately. (See "Management of diabetes mellitus in hospitalized patients", section on 'Insulin infusion' and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment", section on 'Insulin'.)

While several devices are available for monitoring glucose, none have proven efficacy over the other [52-54].

●While most clinicians agree that such glycemic control is a desirable intervention, the optimal blood glucose range is as follows:

•For hyperglycemic critically ill children and adults, we recommend againstusing a stringent intensive insulin therapy regimen to achieve a target blood glucose range of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) ((Grade 1A) for adults;(Grade 1B) for children). Rather, we suggest a blood glucose target of 140 to 180 mg/dL (7.7 to 10 mmol/L) rather than a more stringent target or a more liberal target (eg, 180 to 200 mg/dL [10 to 11.1 mmol/L]) (Grade 2C). This preference is based upon clinical trials in critically ill children and adults that suggest that IIT is not beneficial and is associated with an increased risk of severe hypoglycemia. (See 'Glycemic control' above and 'General approach'above.)

•To achieve the target blood glucose in adult patients, we minimize use of intravenous fluids (IVF) that contain glucose and administer insulin only when necessary. A widely accepted insulin regimen has not been established but short-acting insulin is preferred. The same basic principles apply in pediatric patients with the exception that children (particularly young children) generally require dextrose in maintenance IVF to ensure adequate glucose delivery to avoid hypoglycemia and provide nutrition. Other sources of glucose (eg, IV medications) should be limited in critically ill children. (See 'General approach'above.)

•Careful monitoring of blood glucose is necessary to achieve glycemic control while avoiding the potential harmful effects of hypoglycemia. (See 'General approach' above and 'Hypoglycemia' above.)