

INTENSIVE INSULIN THERAPY IN THE INTENSIVE CARE UNIT: UPDATE ON CLINICAL IMPACT AND MECHANISMS OF ACTION

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ABSTRACT

Objective: Hyperglycemia is a common feature of the critically ill and has been associated with increased mortality. In this review, we give an overview of studies associating critical illness–induced hyperglycemia with adverse outcome and describe how mortality and morbidity are affected when blood glucose levels are strictly controlled to normoglycemia with intensive insulin therapy.

Results: Maintaining normoglycemia with intensive insulin therapy improves survival rates and reduces morbidity in prolonged critically ill patients in both surgical and medical intensive care units (ICUs), as shown by 2 large randomized controlled studies. Prevention of cellular glucose toxicity by strict glycemic control appears to play a predominant role, but other metabolic and nonmetabolic effects of insulin also seem to contribute to the clinical benefits of this therapy.

Conclusion: These data support the generalized implementation of a strict blood glucose control management with intensive insulin therapy in adult surgical as well as medical ICU patients. (*Endocr Pract.* 2006;12[Suppl 3]:14-21)

Abbreviations:

GLUT-4 = glucose transporter 4; **ICU** = intensive care unit; **NO** = nitric oxide

INTRODUCTION

Patients who are critically ill have a high risk of death and suffer from substantial morbidity. The hypermetabolic stress response that usually follows any type of major trauma or acute illness is associated with hyperglycemia and insulin resistance, often referred to as “stress diabetes” or “diabetes of injury” (1,2). In critically ill patients, even those who had not been diagnosed previously with diabetes, glucose uptake is reduced in peripheral insulin-sensitive tissues, whereas endogenous glucose production is increased, resulting in hyperglycemia. It was generally accepted that moderate hyperglycemia in critically ill patients is beneficial by ensuring an extra supply of glucose as a source of energy to organs that do not require insulin for glucose uptake, among which are the brain and the immune system. However, an increasing body of evidence has shown that higher degrees of hyperglycemia upon admission, as well as longer duration of hyperglycemia during critical illness, are associated with poorer outcomes. Evidence against the concept of tolerating hyperglycemia during critical illness came only recently, from 2 large randomized controlled trials: one in a group of surgical intensive care patients (3), the other in exclusively medical intensive care patients (4). Both studies showed that tight blood glucose control (below 110 mg/dL) with insulin therapy significantly improves morbidity and mortality, with the most striking benefits obtained when intensive insulin therapy is given for at least a few days. Current evidence supports a key role for blood glucose control in mediating these outcome benefits, whereas glucose-independent actions of insulin also may contribute to a certain extent (5).

HYPERGLYCEMIA IS ASSOCIATED WITH ADVERSE OUTCOME OF CRITICAL ILLNESS

The development of stress-induced hyperglycemia has been shown to be associated with several clinically important problems in a wide array of patients with severe illness or injury. An increasing number of studies have shown that the degree of hyperglycemia upon admission, as well as the duration of hyperglycemia during critical illness, correlates

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with clinical outcome. In a group of patients with severe brain injury, hyperglycemia was associated with longer duration of hospital stay, poorer neurologic status, pupil reactivity, higher intracranial pressure, and lower survival rates (6,7). Among severely burned children, the incidence of bacteremia and fungemia, the number of skin-grafting procedures, and the risk of death were higher for hyperglycemic patients than for normoglycemic patients (8). In trauma victims, elevated glucose levels early after injury have been associated with infectious morbidity, lengthier stays in the intensive care unit (ICU) and hospital, and higher mortality rates (9,10). Furthermore, this effect appeared to be independent of the associated shock or the severity of injury (10). Trauma patients with persistent hyperglycemia had a significantly greater degree of morbidity and mortality (11). A meta-analysis of myocardial infarction showed an association between hyperglycemia and increased risks of congestive heart failure or cardiogenic shock and in-hospital mortality (12). Higher blood glucose levels predicted a higher risk of death after stroke and poor functional recovery in those patients who survived (13). A retrospective review of a heterogeneous group of critically ill patients indicated that even a modest degree of hyperglycemia occurring after admission to the ICU was associated with a substantial increase in hospital mortality (14). A retrospective study of nondiabetic pediatric patients who were critically ill demonstrated that hyperglycemia was associated with higher in-hospital mortality rates and longer lengths of stay (15).

In spite of this long-standing clear link between hyperglycemia and adverse outcome of acute illnesses, there had been no proof of causality for this association. Such proof requires randomized controlled clinical studies, and these were published only recently.

BLOOD GLUCOSE CONTROL WITH INTENSIVE INSULIN THERAPY IMPROVES OUTCOME OF CRITICAL ILLNESS

The first landmark prospective, randomized, controlled clinical trial of intensive insulin therapy in a large group of patients admitted to the ICU after extensive or complicated surgery or trauma showed major clinical benefits on morbidity and mortality (3). In the conventional management of hyperglycemia, insulin was administered to the patients only when blood glucose levels exceeded 220 mg/dL, with the aim of keeping concentrations between 180 and 200 mg/dL, which resulted in mean blood glucose levels of 150 to 160 mg/dL (hyperglycemia). For patients treated with intensive insulin therapy, insulin was administered by infusion and titrated to maintain blood glucose levels between 80 and 110 mg/dL, which resulted in mean levels of 90 to 100 mg/dL (normoglycemia). This intervention appeared safe because, despite a higher incidence of brief episodes of hypoglycemia, no hypoglycemia-induced adverse events

were reported. Maintaining normoglycemia with insulin during the ICU stay lowered the in-hospital mortality rate strikingly, by 34% (absolute mortality was reduced from 10.9% to 7.2%). The benefit was most pronounced among patients who required intensive care for more than a few days (in-hospital mortality was reduced from 20.6% to 13.6% among patients in ICU for at least a third day [Fig. 1] and from 26.3% to 16.8% among patients in ICU for at least a fifth day). Besides saving lives, insulin therapy largely prevented several critical illness-associated complications. The development of bloodstream infections was reduced by 46%, and acute renal failure requiring dialysis or hemofiltration was reduced by 41%. The incidence of bacteremia decreased by 46%, and critical illness polyneuropathy was reduced by 44%. The number of red blood cell infusions decreased by 50%. Patients also were less dependent on prolonged mechanical ventilation and needed fewer days in intensive care (average ICU stay decreased from 8.8 days to 6.6 days). Although a large number of patients in this study recovered from complicated cardiac surgery, the clinical benefit of this therapy was equally apparent for most other diagnostic subgroups. Among patients with isolated brain injury, tight glycemic control protected the central and peripheral nervous system from secondary insults and improved long-term rehabilitation (16).

Important confirmation of the clinical benefits of intensive insulin therapy was demonstrated recently by a large randomized controlled trial. In this trial, the Leuven protocol of glycemic control with insulin in adult critically ill surgical patients (3) was effective in an exclusively medical adult ICU population (4). Based on the results from the surgical ICU study, this medical ICU study had been powered to detect a reduction of in-hospital mortality among patients treated for at least 3 days in the ICU. In this exclusively medical ICU population, in which sepsis is the most common trigger for ICU admission, intensive insulin therapy during the ICU stay of all 1,200 intention-to-treat patients significantly reduced morbidity, as indicated by prevention of kidney injury, shortening of time on mechanical ventilation, and shorter lengths of stay in the ICU and hospital. The in-hospital mortality rate decreased from 40.0% to 37.3%; however, this difference was not significant, which was not surprising because the study was not powered for a mortality effect among all patients admitted to the medical ICU. In the target group for which the study was powered, the 767 patients treated for at least 3 days, intensive insulin therapy not only improved morbidity but also reduced mortality. Morbidity benefits in the long-stay subgroup included prevention of kidney injury, reduced duration of mechanical ventilation (from a mean of 13.4 days to 10.9 days), shorter ICU stay (from 14.6 days to 12.4 days), and shorter hospital stay (from 43.5 days to 32.9 days), but not prevention of bloodstream infections or transfusion requirements. Among the long-stay patients, in-hospital mortality was reduced significantly, from 52.5%

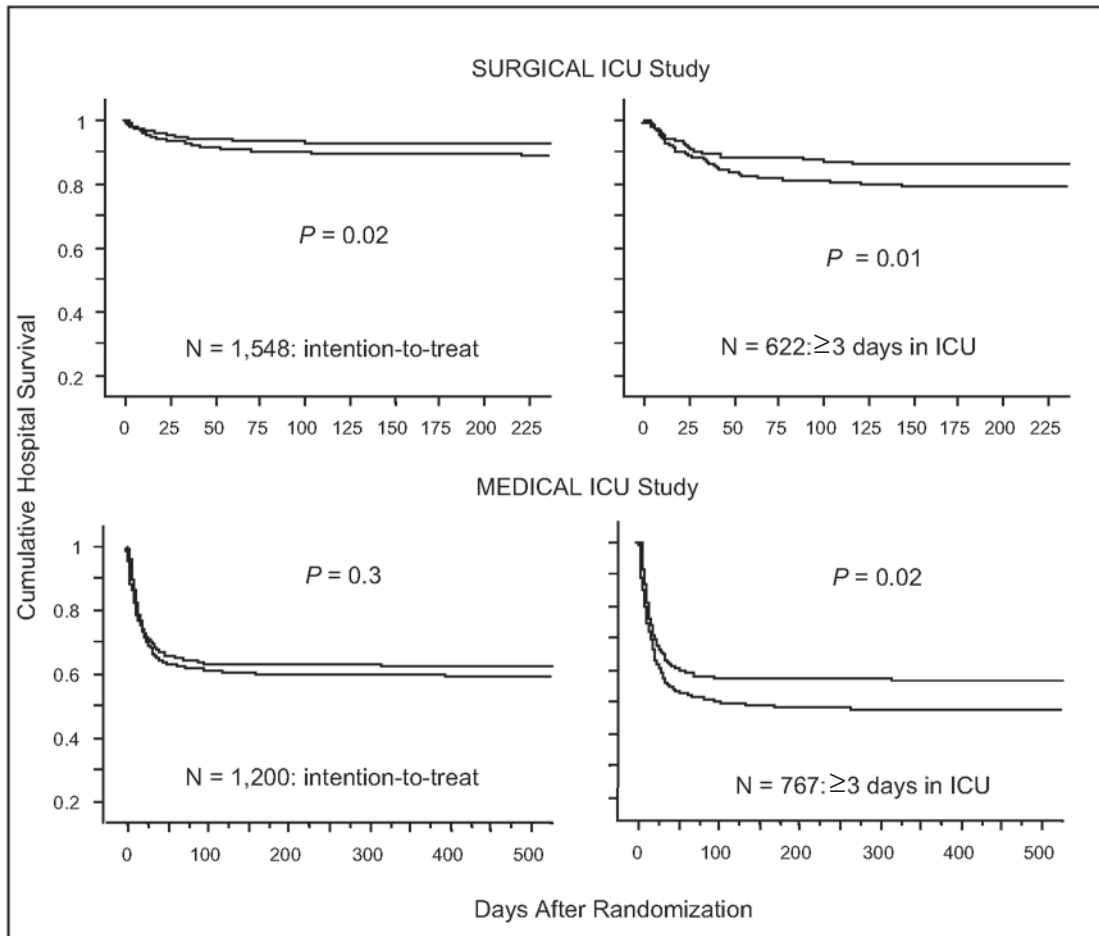


Fig. 1. Intensive insulin therapy saves lives. Kaplan-Meier hospital survival plots of patients from the 2 Leuven studies who received intensive insulin treatment (blood glucose maintained below 110 mg/dL; *thick line*) or conventional treatment (insulin administration only when blood glucose exceeded 220 mg/dL; *thin line*) in the ICU. The *upper panels* display results from the surgical ICU study (3); the *lower panels* show results from the medical ICU study (4). Right panels are data for long-stay (≥ 3 days) ICU patients only. *P* values were determined using the Mantel-Cox log-rank test of proportional hazard regression analysis. The surgical ICU study was powered to detect a mortality effect among all intention-to-treat patients; the medical ICU study was powered to detect a mortality effect among long-stay patients only.

to 43.0%. These data indicate that the preventive effect on severe infections, observed in the surgical study, is not the most important pathway by which mortality is reduced with intensive insulin therapy. The available data also indicate that a morbidity benefit is obtained among all-comers in medical ICU, but in order to obtain a mortality benefit, at least a few days of intensive insulin therapy is required. Future larger studies, adequately powered to detect a benefit on mortality among all-comers in medical ICU, are required. Such studies should include at least 5,000 medical ICU patients.

In “real-life” intensive care medicine, Jamie Krinsley (17) evaluated the impact of implementing strict blood glucose control in a mixed medical/surgical ICU population. A less strict blood glucose control was aimed for, a regimen chosen primarily to avoid inadvertent hypoglycemia. In this setting, insulin therapy lowered mean blood glucose levels from 152 mg/dL (baseline value) to 131 mg/dL in the

protocol period. A comparison with patient data obtained before implementation of the protocol showed a 29.3% reduction in hospital mortality and a 10.8% decrease in length of ICU stay. The incidence of new renal insufficiency was 75% lower, and 18.7% fewer patients required red blood cell transfusion. Again, the number of patients acquiring infections did not change significantly, but the incidence was already low at baseline in this group (17).

A small, prospective, randomized, controlled trial by Grey and Perdrizet (18), conducted in a predominantly surgical ICU, confirmed the beneficial effect of tight blood glucose control on the number of serious infections. In this study, insulin therapy was targeted to glucose levels between 80 and 120 mg/dL, which resulted in a mean daily glucose level of 125 mg/dL versus 179 mg/dL in the standard glycemic control group. Compared with the conventional approach, intensive insulin therapy was associated with a significant reduction in the incidence of all nosocomial

infections, including intravascular device, bloodstream, intravascular device-related bloodstream, and surgical-site infections (18).

THE RISK OF HYPOGLYCEMIA DURING CRITICAL ILLNESS

In both the surgical and medical ICU randomized studies performed in Leuven, the risk of hypoglycemia (defined as blood glucose level ≤ 40 mg/dL) increased with intensive insulin therapy. Experiencing hypoglycemia in both studies was independently associated with risk of death when assessed by multivariate logistic regression analysis. Hence, it cannot be excluded from these clinical studies that some benefits of tight blood glucose control came at the expense of certain risks of hypoglycemia. However, there were no obvious clinical problems associated with these brief episodes of biochemical hypoglycemia in either of the studies. Clearly, the development of accurate blood glucose monitoring in a continuous way, and closed-loops systems for computer-assisted blood glucose control in the ICU, will help avoid any eventual side effect that could be induced by hypoglycemia.

PATHOPHYSIOLOGY OF HYPERGLYCEMIA DURING CRITICAL ILLNESS

The stress imposed by any type of acute illness or injury leads to the development of insulin resistance, glucose intolerance, and hyperglycemia. Hepatic glucose production is up-regulated in the acute phase of critical illness, despite high blood glucose levels and abundantly released insulin. Elevated levels of cytokines, growth hormone, glucagons, and cortisol might play a role in the increased gluconeogenesis (19-23). Several effects of these hormones oppose the normal action of insulin, resulting in increased lipolysis and proteolysis, which provides substrates for gluconeogenesis. Catecholamines, which are released in response to acute injury and often are administered as vasoactive drugs in the ICU, enhance hepatic glycogenolysis and inhibit glycogenesis (24). Apart from the up-regulated glucose production, glucose uptake mechanisms are affected during critical illness and contribute to the development of hyperglycemia. Due to immobilization of the critically ill patient, exercise-stimulated glucose uptake in skeletal muscle is supposedly absent (25,26). Furthermore, because of impaired insulin-stimulated glucose uptake by the glucose transporter 4 (GLUT-4), as well as impaired glycogen synthase activity, glucose uptake in the heart, skeletal muscle, and adipose tissue is compromised (27-30). However, total body glucose uptake is increased, but is accounted for by tissues that are not dependent on insulin for glucose uptake, such as the brain and blood cells (1,31). The higher levels of insulin, impaired peripheral glucose uptake, and elevated hepatic glucose production reflect the development of insulin resistance during critical illness.

The mechanism by which insulin therapy lowers blood glucose in critically ill patients is not completely clear. It is believed that these patients suffer from both hepatic and skeletal-muscle insulin resistance. However, data from liver and skeletal-muscle biopsies, harvested from nonsurvivors in the Leuven study, suggest that glucose levels are lowered mainly via stimulation of skeletal-muscle glucose uptake. Indeed, insulin therapy did increase mRNA levels of GLUT-4, which controls insulin-stimulated glucose uptake in muscle, and of hexokinase-II, the rate-limiting enzyme in intracellular insulin-stimulated glucose metabolism (32). On the other hand, hepatic insulin resistance in these patients is not overcome by insulin therapy. The hepatic expression of phosphoenolpyruvate carboxykinase, the rate-limiting enzyme in gluconeogenesis, and of glucokinase, the rate-limiting enzyme for insulin-mediated glucose uptake and glycogen synthesis, were unaffected by insulin therapy (32,33). Moreover, circulating levels of insulin-like growth factor binding protein-1, normally under inhibitory control of insulin, also were refractory to therapy in the total population of survivors and nonsurvivors (32).

A KEY ROLE OF PREVENTING GLUCOSE TOXICITY WITH INTENSIVE INSULIN THERAPY

It is striking that during the relatively short period that patients need intensive care, avoiding even a moderate level of hyperglycemia with insulin improves the most feared complications of critical illness. Thus, it appears that hyperglycemia is much more acutely toxic in critically ill patients than in healthy individuals, whose cells are protected by down-regulation of glucose transporters (34). This acute toxicity of high levels of glucose in critical illness might be explained by an accelerated cellular glucose overload and the more pronounced toxic side effects of glycolysis and oxidative phosphorylation (35).

Hepatocytes, gastrointestinal mucosal cells, pancreatic beta cells, renal tubular cells, alveolar cells, endothelial cells, immune cells, and neurons are insulin-independent for glucose uptake, which is mediated mainly by the glucose transporters GLUT-1, GLUT-2, and GLUT-3 (1). Cytokines, angiotensin II, endothelin-1, vascular endothelial growth factor, transforming growth factor- β , and hypoxia, all induced in critical illness, have been shown to up-regulate expression and membrane localization of GLUT-1 and GLUT-3 in different cell types (36-40). This up-regulation might overrule the normal down-regulatory protective response against hyperglycemia. Moreover, GLUT-2 and GLUT-3 allow glucose to enter cells directly in the equilibrium with the elevated extracellular glucose level, which is present in critical illness (41). Therefore, one would expect increased glucose toxicity in tissues where glucose uptake is mediated by non-insulin-dependent transport.

Hyperglycemia has been linked to the development of increased oxidative stress in diabetes, in part due to enhanced mitochondrial superoxide production (42-

44). Superoxide interacts with nitric oxide (NO) to form peroxynitrite, a reactive species able to induce tyrosine nitration of proteins, which affects their normal function (45). During critical illness, cytokine-induced activation of NO synthase increases NO levels, and hypoxia-reperfusion aggravates superoxide production, resulting in more peroxynitrite being generated (45). When cells in critically ill patients are overloaded with glucose, high levels of peroxynitrite and superoxide are to be expected, resulting in inhibition of the glycolytic enzyme GAPDH, and mitochondrial complexes I and IV (42).

We recently demonstrated that prevention of hyperglycemia with insulin therapy protected both ultrastructure and function of the hepatocytic mitochondrial compartment of critically ill patients, but no obvious morphologic or pronounced functional abnormalities were detected in skeletal muscle of critically ill patients (46). Mitochondrial dysfunction with disturbed energy metabolism is a likely cause of organ failure, the most common cause of death in the ICU. Prevention of hyperglycemia-induced mitochondrial dysfunction in other tissues that allow glucose to enter passively might explain some of the protective effects of intensive insulin therapy in critical illness.

IMPACT OF OTHER METABOLIC AND NONMETABOLIC EFFECTS OF INTENSIVE INSULIN THERAPY

As in diabetic patients (47), the lipid metabolism of critically ill patients is strongly deranged. Most characteristic for the dyslipidemia of critical illness are the elevated triglycerides together with very low levels of HDL and LDL cholesterol (48-50). Insulin therapy almost completely reversed the hypertriglyceridemia and elevated HDL and LDL and the level of cholesterol associated with these lipoproteins (32). Insulin treatment also decreased serum triglycerides and free fatty acids in burned children (51). Multivariate logistic regression analysis showed that improvement of the dyslipidemia with insulin therapy explained a significant part of the reduced mortality and organ failure in critically ill patients (32). Given the important role of lipoproteins in the transportation of lipid components (cholesterol, triglycerides, phospholipids, lipid-soluble vitamins) and endotoxin scavenging (52-54), a contribution to improved outcome might well be expected.

Critically ill patients become severely catabolic, with loss of lean body mass, despite adequate enteral or parenteral nutrition. Intensive insulin therapy might attenuate this catabolic syndrome of prolonged critical illness because insulin exerts anabolic actions (55-58). Intensive insulin treatment has resulted in higher total protein content in skeletal muscle of critically ill patients (46) and prevented weight loss in a rabbit model of prolonged critical illness (59).

Intensive insulin therapy prevented excessive inflammation, illustrated by decreased C-reactive protein (CRP)

and mannose-binding lectin levels (60), independent of its preventive effect on infections (3). Insulin therapy also attenuated the CRP response in an experimental animal model of prolonged critical illness, which was induced by third-degree burn injury (59). Moreover, critically ill rabbits showed an increased phagocytosis capacity of monocytes and their ability to generate an oxidative burst when blood glucose levels were kept normal (59). In burned children, administration of insulin resulted in lower pro-inflammatory cytokines and proteins, whereas the anti-inflammatory cascade was stimulated, although these effects were largely seen only late after the traumatic stimulus (51). Insulin treatment attenuated the inflammatory response in thermally injured rats and endotoxemic rats and pigs (61-63). In addition to these anti-inflammatory effects of insulin, the prevention of hyperglycemia appears to be crucial as well. Hyperglycemia inactivates immunoglobulins by glycosylation, and therefore contributes to the risk of infection (64). High glucose levels also negatively affected polymorphonuclear neutrophil function and intracellular bactericidal and opsonic activity (65-68).

Critical illness also resembles diabetes mellitus in its hypercoagulation state (69,70). Many conditions can contribute to the hypercoagulation involved in diabetes mellitus, including vascular endothelium dysfunction, elevated platelet activation, increased clotting factors, and inhibition of the fibrinolytic system. (71-75). Insulin therapy has been shown to protect the myocardium and improve myocardial function after acute myocardial infarction, during open heart surgery, and in congestive heart failure (76). Prevention of endothelial dysfunction also contributed to the protective effects of insulin therapy in critical illness, in part via inhibition of excessive iNOS-induced NO release (77) and by reduction of circulating levels of asymmetric dimethylarginine, which inhibits the constitutive enzyme eNOS and hence the production of endothelial NO (78).

GLUCOSE CONTROL OR INSULIN?

Multivariate logistic regression analysis of the results of the first Leuven study indicates that blood glucose control, and not the insulin dose administered, explains most of the beneficial effects of insulin therapy on outcome of critical illness (5). It appeared crucial to reduce blood glucose levels below 110 mg/dL for the prevention of morbidity such as bacteremia, anemia, and acute renal failure. The level of hyperglycemia also was an independent risk factor for the development of critical illness polyneuropathy (5). Finney et al (79) confirmed the independent association between hyperglycemia and adverse outcome in surgical ICU patients. Our recent experiments in an animal model of critical illness, in which we independently manipulated levels of blood glucose and insulin (80), confirmed the superior role of strict blood glucose control over the glycemia-independent effects of insulin, in obtaining the survival benefit as well as most of the morbidity-reducing benefits.

CONCLUSION

Hyperglycemia in critically ill patients results from altered glucose metabolism. Apart from the up-regulated glucose production (both gluconeogenesis and glycogenolysis), glucose uptake mechanisms also are affected during critical illness and contribute to the development of hyperglycemia. The higher levels of insulin, along with impaired peripheral glucose uptake and elevated hepatic glucose production, reflect the development of insulin resistance during critical illness.

Hyperglycemia in critically ill patients has been associated with higher mortality rates. Simply maintaining normoglycemia with insulin therapy improves survival and reduces morbidity in surgical and medical ICU patients, as shown by the results of 2 large randomized controlled studies, with the most pronounced benefit being for patients treated at least 3 days. These results of these randomized clinical studies have been confirmed in real-life intensive care of a heterogeneous patient population admitted to a mixed medical/surgical ICU. The prevention of glucose toxicity by strict glycemic control appears to be crucial, although other metabolic and nonmetabolic effects of insulin, independent of glycemic control, also may contribute to the clinical benefits.

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