

CLINICAL PRACTICE

Glycemic Control in the ICU

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 42-year-old man is admitted to the intensive care unit (ICU) with an acute exacerbation of asthma associated with community-acquired pneumonia. He is treated with cefotaxime and azithromycin, nebulized albuterol, and intravenous hydrocortisone. He has no known history of diabetes mellitus. Shortly after admission, his arterial glucose concentration is 105 mg per deciliter (5.8 mmol per liter), and on the next day, it has increased to 195 mg per deciliter (10.8 mmol per liter). His glycated hemoglobin level is 5.3%. Should this elevated glucose level be treated?

THE CLINICAL PROBLEM

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Stress hyperglycemia is the elevation of blood glucose in the presence of acute illness.¹ Factors contributing to hyperglycemia in critical illness include the release of stress hormones (e.g., epinephrine and cortisol), the use of medications such as exogenous glucocorticoids and catecholamines, and the release of mediators in cases of sepsis or surgical trauma (Fig. 1), all of which inhibit insulin release and action, thereby enhancing gluconeogenesis, inhibiting glycogen synthesis, and impairing insulin-mediated glucose uptake by tissues. Intravenous dextrose, commonly used in parenteral nutrition and antibiotic solutions, also contributes to hyperglycemia.²

Hyperglycemia in the ICU has not consistently been shown to portend a worse prognosis in patients with preexisting diabetes. Conversely, hyperglycemia has been linked with worse outcomes in patients not known to have diabetes who are admitted to the ICU³ and specifically in those with an acute coronary syndrome⁴ or stroke.⁵ Often, this association reflects the severity of the illness (i.e., a greater likelihood of hyperglycemia in sicker patients), but hyperglycemia itself may also contribute to the burden of disease. Observational data indicate that for glucose values in the range of 79 to 200 mg per deciliter (4.4 to 11.0 mmol per liter), the duration of exposure to higher glucose concentrations is inversely associated with survival.³

Several mechanisms have been hypothesized to explain how hyperglycemia may cause harm (Fig. 1). Among the potential mechanisms, an increased susceptibility to sepsis is perhaps the foremost contributor to a poor outcome in critically ill patients.⁶ However, there are insufficient data to determine the threshold at which an elevated glucose concentration has deleterious effects on tissue.

STRATEGIES AND EVIDENCE

EVALUATION

Traditionally, acute hyperglycemia was defined as a random glucose concentration of more than 200 mg per deciliter,² but in 2010, the American Diabetes Association proposed a threshold of 140 mg per deciliter (7.8 mmol per liter).⁷ In patients not known to have diabetes, glycated hemoglobin should be measured; an elevated level

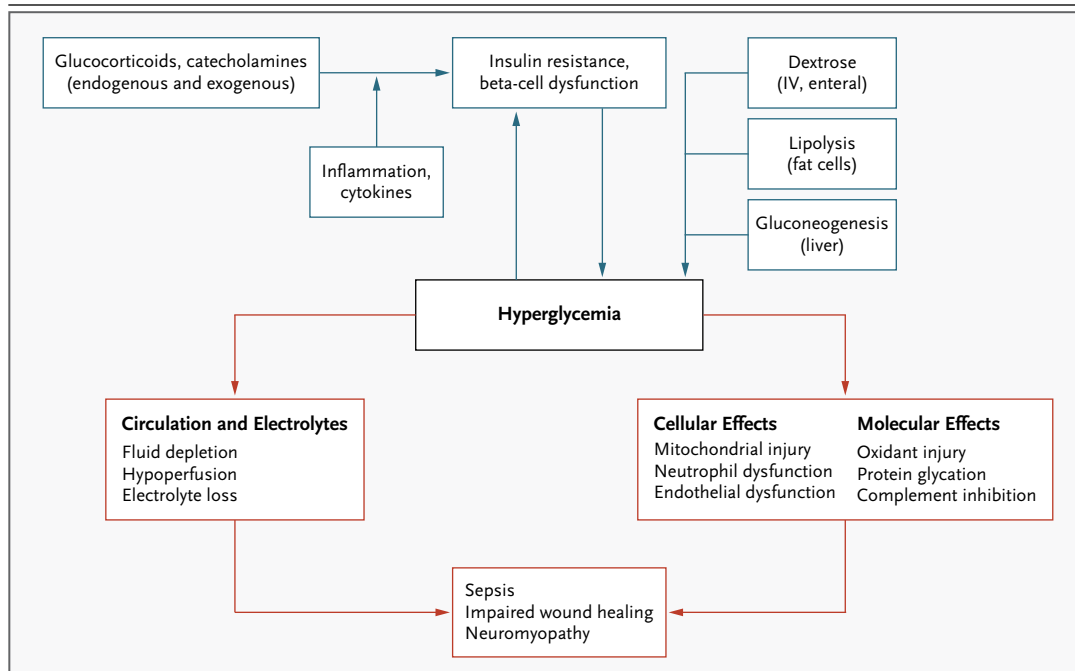


Figure 1. Causes and Effects of Stress Hyperglycemia.

Stress hyperglycemia can be caused by exogenous administration or endogenous production of glucose and by insulin resistance or reduced secretion of insulin owing to beta-cell dysfunction. The resulting hyperglycemia can potentiate insulin resistance. The consequences of elevated glucose levels may be manifested at the molecular or cellular level, combining to cause tissue abnormalities that include sepsis, impaired wound healing, and neuromyopathy. IV denotes intravenous.

(above 6.5%) indicates preexisting diabetes, which should be managed with appropriate long-term follow-up.⁷

MANAGEMENT

Studies of Intensive Insulin Therapy

Before 2001, in the absence of evidence that tight glucose control could influence the risk of illness or death, little attention was paid to control of hyperglycemia in the ICU. This section provides a brief review of the research examining the effects of normalizing elevated glucose levels on outcomes in critically ill patients.^{6,8-14} The range targeted is 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter).

A single-center trial in Leuven, Belgium,⁶ that involved 1548 patients, most of whom had undergone cardiac surgery, provided the first evidence of a benefit of tight glucose control in the ICU. Patients were randomly assigned to intensive insulin therapy (target glucose range, 80 to 110 mg per deciliter) or standard care (target glucose range, 180 to 200 mg per deciliter [9.9 to 11.0 mmol per liter]). In the group receiving in-

tensive insulin therapy, the targeted glucose levels were achieved (mean [±SD], 103±19 mg per deciliter [5.7±1.1 mmol per liter]) and resulted in reduced mortality in the ICU, as compared with the group receiving standard care (4.6% vs. 8%). However, serious hypoglycemia (glucose level, <40 mg per deciliter [2.2 mmol per liter]) occurred in 5% of the patients receiving intensive therapy, a finding that is cause for concern. In addition, the study was not blinded, and the mortality in the control group was high relative to that in other cardiac surgical centers.

A subsequent single-center, nonblinded trial⁹ from the same group included 1200 medical ICU patients who were expected to require intensive care for more than 3 days. The target glucose levels in the group assigned to intensive insulin therapy and the control group were identical to the target in the previous study,⁶ and the glucose concentration achieved with intensive therapy was similar (110±19 mg per deciliter). In contrast to the earlier study, intensive insulin therapy did not reduce overall mortality and was associated with a high rate of serious hypoglycemia (18.7%).

In secondary analyses, the intensive-therapy group was found to have a lower rate of acquired renal impairment (5.9% vs. 8.9%), a significantly shorter duration of mechanical ventilation, and significantly shorter stays in the ICU and the hospital than the control group.

The second trial differed from the first not only in terms of the ICU setting (medical vs. surgical in the first study) but also in its approach to nutrition, which was less intensive — in the first study, the use of parenteral nutrition was predominant. In addition, mortality rates in the control group in the second study were lower than expected (on the basis of scores on the Acute Physiology and Chronic Health Evaluation [APACHE] II), whereas mortality rates in the control group in the first study were higher than expected. A post hoc analysis in the second study suggested that patients whose ICU stay was longer than 3 days benefited from intensive insulin therapy (lower mortality and fewer bloodstream infections).⁸ However, the length of the ICU stay could not be accurately predicted on admission to the ICU, and the possibility of better outcomes for patients receiving intensive insulin therapy who had a longer stay (>3 days) was counterbalanced by potentially worse outcomes with this therapy among those with shorter stays.¹⁵

Four additional studies (two multicenter trials and two single-center trials, collectively including more than 2600 patients at 41 centers) examined mixed populations of both medical and surgical ICU patients.^{9-11,13} All four studies involved target (and achieved) glucose levels in the control and intensive-therapy groups^{9-11,13} that were similar to those in the Leuven study of glucose control in medical ICUs.⁸ Overall, intensive insulin therapy was found to have no significant effect on mortality and resulted in a high incidence of hypoglycemia (8 to 28%). Aside from a possible increase in vasopressor use in one study,¹³ there were also no benefits associated with intensive insulin therapy with respect to rates of secondary outcomes (including renal impairment and duration of mechanical ventilation or length of stay).^{9-11,13}

The largest trial of tight glucose control in the ICU, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (ClinicalTrials.gov number, NCT00220987), included 6104 patients — more than in all the other studies combined

— and 42 centers.¹² As compared with the control group, the intensive-therapy group in this trial had an absolute increase in mortality of 2.6 percentage points ($P=0.02$) and an increased incidence of hypoglycemia (6.8% vs. 0.5%). The glucose target with intensive therapy was similar to that in the other studies, but the glucose levels achieved were higher (118 ± 25 mg per deciliter [6.6 ± 1.4 mmol per liter]), and the target for the control group was lower (<180 mg per deciliter). The mean level of glucose reported for the control group — 145 mg per deciliter (8.0 mmol per liter) — was achieved with substantial quantities of insulin¹²; thus, in this study, the treatment provided in the control group represented moderate — not lax — glucose control. There may have been fundamental differences between this study population and that in the first study suggesting a benefit from glucose control,⁶ since the mortality rate in the control group in the NICE-SUGAR study (24.9%) was lower than that predicted by the APACHE II score (39%). In addition, the nutrition regimen in the NICE-SUGAR study was less aggressive than most of the regimens in the other prospective studies and was predominantly enteral.

The results of a randomized trial of intensive insulin therapy with glucocorticoids for the treatment of septic shock showed no reduction in mortality and also a higher incidence of hypoglycemia in the intensive-therapy group, as compared with the control group (16.4% vs. 7.8%). There were no other differences in morbidity.¹⁴

A meta-analysis of 26 randomized trials (many with less ambitious glucose targets than those in the trials discussed above) that included more than 13,500 patients showed that intensive insulin therapy had no overall effect on mortality and resulted in an incidence of hypoglycemia that was six times as high as that among patients not receiving intensive therapy. The analysis did, however, raise the possibility of reduced mortality among surgical ICU patients (relative risk, 0.63; 95% confidence interval [CI], 0.44 to 0.91).¹⁶ A more recent meta-analysis restricted to the seven largest randomized trials (including more than 11,000 patients), in six of which the target glucose level was 80 to 110 mg per deciliter, showed that intensive insulin therapy provided no survival benefit and was associated with increased morbidity.¹⁷

These findings are consistent with observa-

tional data from hospitals in which intensive insulin therapy has been incorporated into ICU care. For example, a cohort study of more than 10,000 patients, comparing outcomes before and after institution of a policy of intensive insulin therapy, showed that the incidence of hypoglycemia was four times as great after the policy was implemented, with no survival benefit (odds ratio for death, 1.15; 95% CI, 0.98 to 1.35).¹⁸

In summary, the preponderance of available evidence suggests that intensive insulin therapy, as compared with standard therapy, does not provide an overall survival benefit, may increase mortality, and is associated with a higher incidence of hypoglycemia. Benefits in terms of secondary outcomes (e.g., renal function and length of ICU or hospital stay) were reported by the Leuven group^{7,9} but were not seen in subsequent trials. The basis for the different outcomes is unclear but may be related to differences among the studies in characteristics of the patients and features of care.

Glucose Monitoring

Glucose can be measured in blood obtained from a variety of sites (e.g., by means of intra-arterial or venous catheters or a fingerstick device). Care should be taken to ensure that the samples have not been contaminated with intravenous solutions. Point-of-care bedside glucometers may be inaccurate (by more than 20%), particularly when used to assess samples from patients with lower glucose levels¹⁹ or to assess fingerstick capillary samples from patients with tissue edema (which has a diluting effect), hypoperfusion, or anemia. Although some ICUs report that these devices are reasonably accurate when blood from a catheter is used,⁶ standardization of the technology is difficult. Laboratory analysis of plasma is the best means of measuring blood glucose levels, but this approach is too slow for use in the ICU. Many ICUs use blood gas analyzers that are highly accurate; if turnaround time can be minimized, this method offers a very practical solution.¹⁹

Since hypoglycemia occurs even when there is frequent (i.e., hourly) monitoring by experienced teams,²⁰ it may be worthwhile to consider new technologies, such as subcutaneous glucose sensors, that produce glucose readings every 5 minutes. However, these sensors monitor glucose levels in interstitial fluid, which can lag behind blood levels; thus, in the case of evolving hypoglycemia, the degree of hypoglycemia may be substantially

greater than indicated.²¹ Continuous intravascular glucose sensors, currently in development, would allow for real-time monitoring, but the need for this technology is less critical when the target glucose range is less stringent than 80 to 110 mg per deciliter.

Insulin Infusion

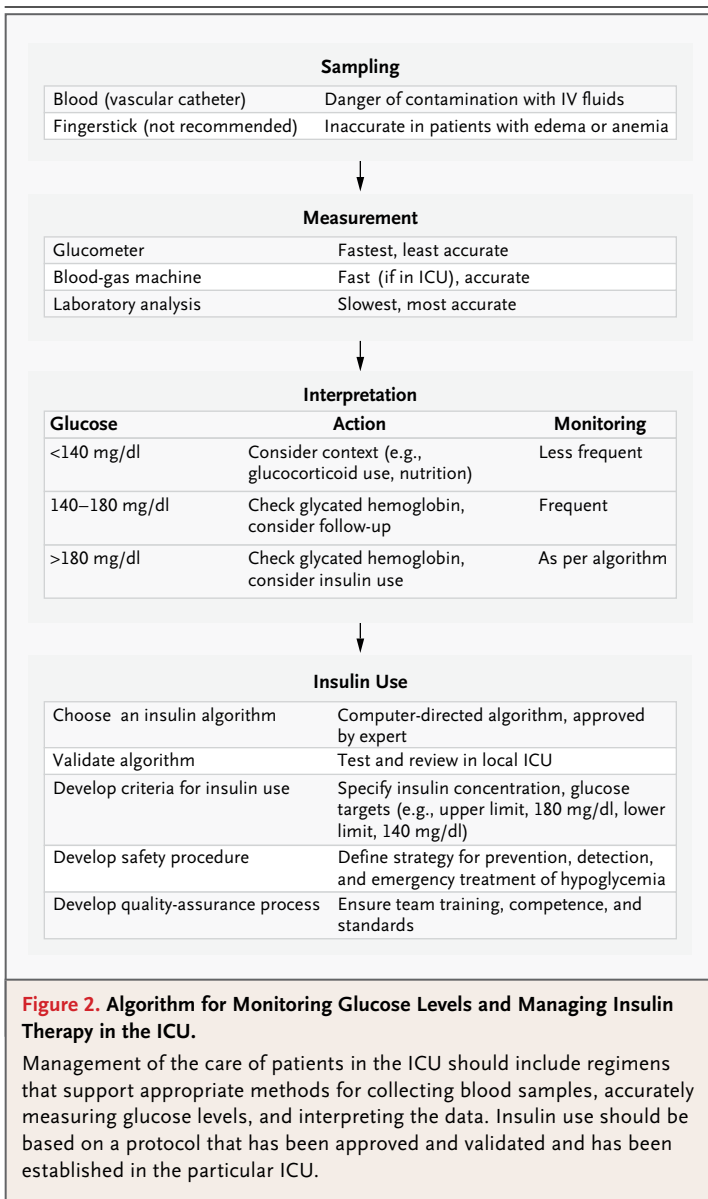
An insulin-infusion protocol needs to be validated and used in the context of ICU practice (Fig. 2). Computer-directed algorithms are effective²² and should be managed by nursing staff.²³ A variety of protocols are available for ICUs intending to control plasma glucose levels in the range of 80 to 110 mg per deciliter. Given the questionable benefits and the risks of such intensive control, a prudent alternative is to use a validated algorithm that specifies a target glucose level below 180 mg per deciliter (10.0 mmol per liter) and incorporates measurement of the actual glucose concentration as well as its rate of change.²² In many ICUs, staffing is an important limitation; the risk of hypoglycemia with insulin therapy has been reported to be increased when nursing schedules are intense and fatigue is prevalent.²⁴ In addition, since insulin is usually administered as an intravenous infusion in the ICU, conversion to subcutaneous insulin-injection therapy may be necessary before or at the time of ICU discharge.²⁵

AREAS OF UNCERTAINTY

GLUCOSE VARIABILITY

Changes in the measured level of blood glucose, termed glucose variability, are usually expressed as the standard deviation around the mean glucose value or as the mean amplitude of glycemic excursions.²⁶ Even when conventional glucose ranges are targeted, wide glycemic variation is an independent predictor of an increased risk of death,²⁷ regardless of the glucose level.²⁸ These observations may reflect an association between the degree of lability and the severity of illness, but it is also conceivable that the association is causal. The potential mechanisms are unclear, although it has been proposed that increased oxidative stress may play a role.²⁹

A concern regarding intensive insulin therapy is that it may increase glucose variability,²⁷ especially if a rigid insulin protocol is used. It is premature to recommend a primary target of minimal glucose variability without evidence from



clinical trials, and no prospective trials have addressed the question of whether a reduction in glucose variability results in improved outcomes with intensive insulin therapy.

HYPOGLYCEMIA

It has been suggested that the inability to avoid hypoglycemia, which is independently associated with increased mortality, has obscured the benefit of intensive insulin therapy.²⁷ In addition, the degree of hypoglycemia parallels the increase in the risk of death²⁸; pooled data from the two Leu-

ven studies suggest that severe hypoglycemia is associated with an increase in mortality by a factor of three.³⁰ Severe hypoglycemia (i.e., <40 mg of glucose per deciliter) occurred in up to 28% of patients in trials of intensive insulin therapy,^{6,8-14} and its incidence is likely to be higher in the real world (i.e., outside clinical trials) if a target range of 80 to 110 mg per deciliter is used.

The neurologic consequences of hypoglycemia are difficult to detect in critically ill patients, but they are a real concern. Hypoglycemia can cause acute electroencephalographic alterations,³¹ and at 4 years of follow-up, a subgroup of patients treated with intensive insulin therapy was found to have impairments in quality of life and social functioning, as compared with patients who received conventional treatment.³² The long-term sequelae of iatrogenic hypoglycemia in the ICU are difficult to measure, and the thresholds for harm are not clear.

NUTRITION

In the first Leuven study, which showed that intensive insulin therapy was associated with a survival benefit, parenteral dextrose was an important source of energy.⁶ A recent meta-analysis suggested that intensive insulin therapy was associated with a reduction in mortality only when a high proportion of calories was provided parenterally.¹⁷ This observation suggests that early, parenteral nutrition supplying high-calorie loads may be necessary to avoid hypoglycemic complications of intensive insulin therapy¹⁷ or that intensive insulin treatment may lower the risk of death only when administered in the context of intensive nutritional support. The rates of hypoglycemia reported in the first Leuven trial⁶ were lower than those in the NICE-SUGAR study,¹² in which nutritional support was less aggressive and the use of intravenous dextrose was minimal. Under such conditions, interruption of enteral feeding may have led to more frequent hypoglycemia or greater difficulty with adherence to the insulin-infusion protocol. The use of predominantly enteral feeding¹² is concordant with U.S. guidelines³³ and Canadian guidelines³⁴ for the provision of nutritional support in critically ill patients and is consistent with standard practice in many ICUs. Intensive insulin therapy may be more beneficial when there is a requirement for parenteral nutrition (particularly intravenous dextrose) that is administered concomitantly.

Table 1. Guidelines from Professional Organizations on the Management of Glucose Levels in the ICU.*

Year	Organization	Patient Population	Treatment Threshold	Target Glucose Level <i>mg/dl</i>	Definition of Hypoglycemia	Updated since NICE-SUGAR Trial, 2009†
2009	American Association of Clinical Endocrinologists and American Diabetes Association	ICU patients	180	140–180	<70	Yes
2009	Surviving Sepsis Campaign	ICU patients	180	150	Not stated	Yes
2009	Institute for Healthcare Improvement	ICU patients	180	<180	<40	Yes
2008	American Heart Association	ICU patients with acute coronary syndromes	180	90–140	Not stated	No
2007	European Society of Cardiology and European Association for the Study of Diabetes	ICU patients with cardiac disorders	Not stated	“Strict”‡	Not stated	No

* The guidelines from the organizations listed are available online: American Association of Clinical Endocrinologists and American Diabetes Association, www.aace.com/pub/pdf/guidelines/InpatientGlycemicControlConsensusStatement.pdf; Surviving Sepsis Campaign, www.survivingsepsis.org/About_the_Campaign/Documents/SSC%20Statement%20on%20Glucose%20Control%20in%20Severe%20Sepsis.pdf; Institute for Healthcare Improvement, www.ihl.org/IHI/Topics/CriticalCare/IntensiveCare/Changes/ImplementEffectiveGlucoseControl.htm; American Heart Association, <http://circ.ahajournals.org/cgi/content/short/117/12/1610>; and European Society of Cardiology and European Association for the Study of Diabetes, www.easd.org/easdwebfiles/homepage/escandeasdguidelines.pdf.

† The Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial is reported by Finfer et al.¹³

‡ The guideline recommends “strict blood glucose control with intensive insulin therapy” and refers to studies in which such therapy has target glucose levels of 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter).

GLYCEMIC GOALS

Considerable uncertainty remains regarding the optimal target levels of glucose for patients in the ICU. It is also unclear whether target levels should differ according to the indication for ICU admission or the stage of acute illness.

— of such guidelines to guard against premature reliance on an early, single-center, nonblinded study.⁶

GUIDELINES FROM PROFESSIONAL SOCIETIES

After publication of the report on the initial Leuven study of intensive insulin therapy in 2001,⁶ some professional societies issued guidelines on target glucose levels in the ICU. One set of guidelines suggested a target level of less than 110 mg per deciliter,³⁵ and another a level of less than 150 mg per deciliter (8.3 mmol per liter).³⁶ With publication of the results of subsequent studies, most professional societies have increased the treatment threshold to values above 180 mg per deciliter (Table 1). Target levels are generally between 140 and 180 mg per deciliter, although some guidelines have yet to reflect the more recent data.²⁵ The evolution of these guidelines is reassuring in that they demonstrate responsiveness to accumulating evidence, but it also serves as a cautionary note to the authors — and the readers

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has elevated glucose levels in the context of acute illness. With ongoing use of glucocorticoids and the institution of nutritional support, further elevations in his plasma glucose level can be expected. He has a glycated hemoglobin level of 5.3%, which indicates that he does not have preexisting diabetes. Although the results of randomized trials of intensive insulin therapy in ICU patients have been inconsistent, most of the data do not support the hypothesis of a survival benefit, and some data have suggested increased mortality. All the trials in which the targeted glucose concentration was 80 to 110 mg per deciliter showed increased rates of hypoglycemia. Moreover, marked hyperglycemia itself is associated with increased risks of adverse outcomes. Thus, pending more data to guide the development of optimal glucose levels, we recommend a target of 140 to 180 mg per deciliter (which is in accordance with the most recent

guidelines), with the use of an established, preferably computerized insulin-infusion algorithm and close monitoring of glucose levels (Fig. 2).¹² In consideration of these moderate target levels, we recommend that nutritional support be introduced gradually, preferably by the enteral route,

and that infusion of substantial quantities of intravenous dextrose be avoided.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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