



Better Glycemic Control: How Sweet It Is!

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A ProCE-publication



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Program Description

This educational activity will describe the impact of hyperglycemia in the critical care setting, as well as research on the development of clinical targets for optimal glycemic control. The author, Cathy Moore, will discuss appropriate management of hyperglycemia in critically ill patients, including current authoritative recommendations. She will also describe the benefits of electronic software programs that support individualized dosing protocols and have become the gold standard for insulin infusion management.

Learning Objectives

The target audience for this program is nurses in critical care settings.

After completing this activity, the participant will be able to:

- Identify 3 complications associated with hyperglycemia in the critical care patient
- Discuss current clinical guidelines for targeted blood glucose levels
- Compare current strategies for insulin infusion management

Funding



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Accreditation



Nurses: Nursing credit is provided for this home-study activity through collaboration between ProCE, Inc. and Wild Iris Medical Education, Inc., a provider of continuing education accredited by the American Nurses Credentialing Center's Commission on Accreditation. This activity provides 1.0 contact hour of nurse CE credit.

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About the Author

Cathy M. Moore is Director of Critical Care at Gaston Memorial Hospital of CaroMont Health in Gastonia, N.C. An RN for 27 years, Cathy spent 5 years at the bedside before accepting the manager role of the Intensive Care and Post Intensive Care units. Shortly thereafter, she accepted the director position, uniting intensive care and cardiac services under one leadership. Cathy has facilitated the opening of four new units, including a new Cardiovascular Surgery program and a Heart Failure Therapy Unit; she is currently involved in Trauma III designation. Cathy is a former poster presenter at NTI and delivers lectures in the RN-to-BSN program at the University of North Carolina at Charlotte.



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Gaston Memorial Hospital (Gastonia, N.C.), where an electronic dosing system for adult insulin infusions was implemented in 2009.

Introduction

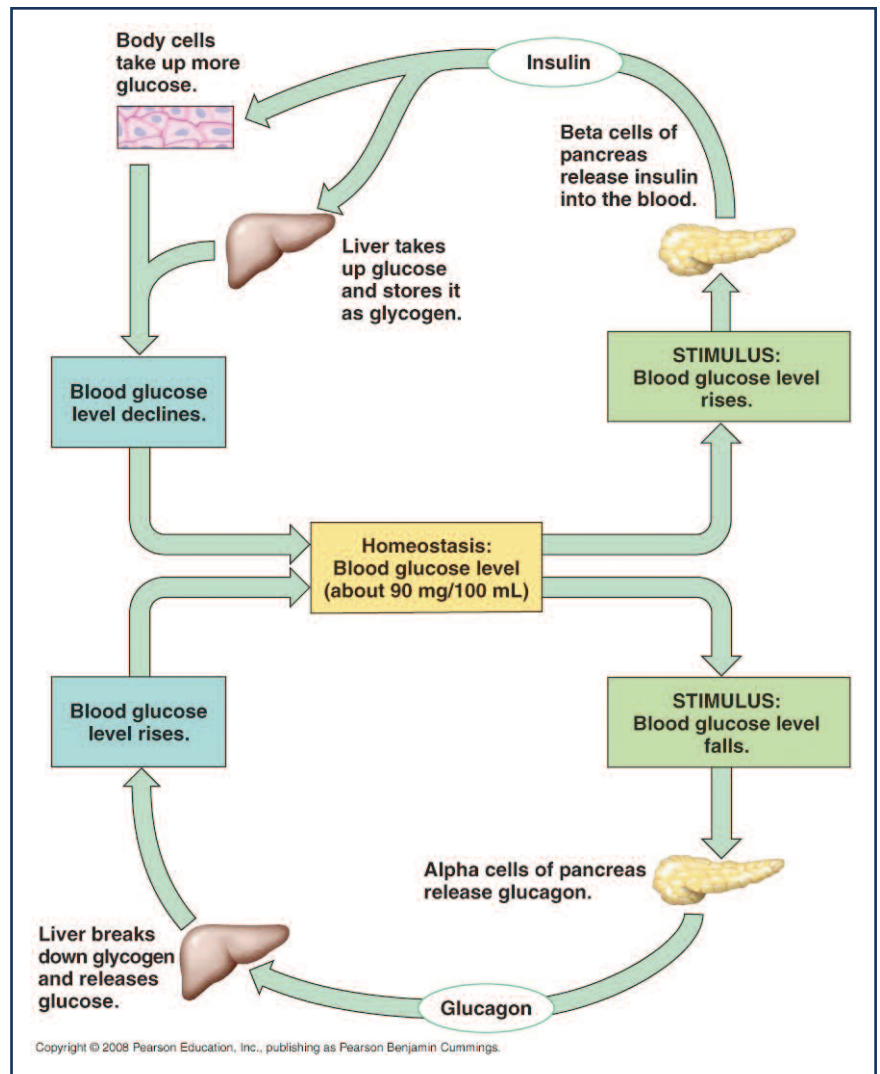
Despite advances in technology and glycemic controls available in medicine today, the development of hyperglycemia in hospitalized patients has risen significantly. In fact, studies cite that as many as one third of all patients admitted to the hospital may experience hyperglycemia.¹ Within this sector of hospitalized patients, another one third do not demonstrate a prior history of diabetes. Recognizing that hyperglycemia is often associated with an increased risk of complications and poor patient outcomes, physicians and other healthcare clinicians seek ways to reduce the risk of hyperglycemia and to optimize blood glucose management in critically ill patients.

Euglycemia versus Hyperglycemia

In healthy people, serum glucose concentration is closely regulated through the homeostasis cycle of insulin versus glucagon (Figure 1). For example, a post-prandial increase in serum glucose stimulates increased pancreatic insulin production. As a result, excess glucose is stored at the cellular level and in the liver as glycogen, thereby reducing the serum glucose level. Conversely, as the body's serum glucose level decreases, glucagon is released by the pancreas. This glucagon stimulates the liver to break down the stored glycogen, releasing glucose to "auto-regulate" serum glucose levels back to normal.

Critically ill patients do not have the ability to auto-regulate serum glucose levels and require insulin therapy to maintain acceptable glucose levels. In fact, insulin resistance has been documented in greater than 80% of critically ill patients.² This inability to regulate serum glucose levels results in uncontrolled hyperglycemia and potentiates myriad undesirable outcomes, including increased risk of infection, impaired immune response, delayed wound healing, increased cost, and increased mortality.³⁻⁵

Figure 1. Negative feedback in glucose homeostasis: insulin versus glucagon.

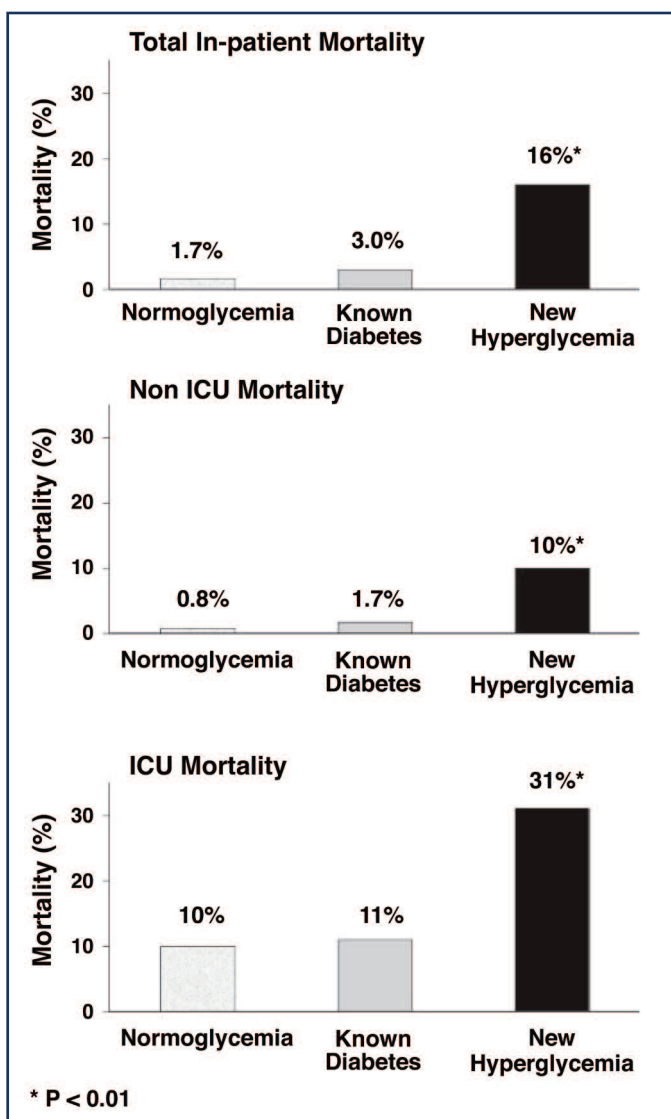


In addition to their own inability to regulate serum glucose levels, hyperglycemia in critically ill patients may have an iatrogenic origin. Hyperglycemia is often pharmacologically induced as a result of steroid or immunosuppressant therapy. Likewise, insufficient insulin dosing may be a factor; clinicians often lack the proper training to effectively manage insulin therapy. Similarly, enteral feeds, total parenteral nutrition (TPN), and dextrose infusions may result in iatrogenic hyperglycemia.⁶

Hyperglycemia and Associated Mortality Rates

In a study by Umpierrez and colleagues,¹ medical records of 2030 consecutive adult patients were studied to determine the prevalence of in-hospital hyperglycemia. As noted earlier, hyperglycemia was present in more than one third (38%) of patients admitted to the hospital, of whom 26% had a known history of diabetes while 12% had no history of the disease. The study also aimed to determine the survival and functional outcomes of these patients. Patients with a new diagnosis of hyperglycemia were more likely to be admitted to the ICU and experienced a longer length of stay than patients with a history of diabetes. Newly diagnosed hyperglycemia was associated with an overall 16% mortality rate, with a significantly higher rate in ICU patients than in non-ICU patients (31% vs 10%, respectively; $P < 0.01$) (Figure 2).

Figure 2. Total inpatient and ICU mortality rates associated with hyperglycemia.¹



Clinical Targets for Serum Glucose Levels

Given the impact of blood glucose levels on mortality rates in the ICU, extensive research has been conducted with the intent of establishing clinically efficacious blood glucose targets.

Among the notable studies that have shaped the development of clinical guidelines in glucose management are the DIGAMI and DIGAMI 2 trials,^{7,8} the Leuven protocol,⁹ and the NICE-SUGAR study.¹⁰

In the mid-1990s, the results of the DIGAMI trial were published.⁷ This trial sought to evaluate the influence of intensive insulin therapy on morbidity and mortality of diabetic patients with myocardial infarction. In this study, patients were randomized into two groups. The control group received standard coronary care treatment for hyperglycemia, using insulin only if deemed absolutely necessary by the physician or if the patient was receiving insulin prior to hospitalization. The experimental group received insulin infusions to maintain blood glucose between 126 and 180 mg/dL. Infusions were maintained for a minimum of 24 hours followed by subcutaneous injections 4 times a day.

With regard to mortality, the infusion group had only a slightly lower in-hospital mortality rate (9.1%) than the control group (11.1%). Mortality rates at 3 months post-MI were 12.4% and 15.6%, respectively. The only significant difference in post-MI mortality was observed at 1 year, with a rate of 18.6% in the infusion group and 26.1% in the control group ($P = 0.0273$). The DIGAMI study was the first to show an impressive reduction in mortality at 1 year for diabetic patients with a history of MI. Factors such as overall improvements in patient care and widespread use of medications such as aspirin, beta-blockers, and thrombolytics are also credited for the reduction in mortality.¹¹

In the DIGAMI 2 trial, patients were randomized into 3 groups:

- Group 1: acute insulin-glucose infusion followed by long-term insulin-based glucose control
- Group 2: acute insulin-glucose infusion followed by standard glucose therapy
- Group 3: routine metabolic management as specified by physician.⁸

The study hoped to extend the findings of the first DIGAMI trial and recruited 1253 participants. After a mean of 2 years,

no significant difference in all-cause mortality was found between Groups 1 and 2 (23.4% and 22.6%, respectively; primary end point) or between Groups 2 and 3 (22.6% and 19.3%, respectively; secondary end point). Researchers concluded that glucose level is a strong, independent predictor of long-term mortality in this patient population. But it does not matter how glucose is lowered (conventionally or with intensive insulin-based treatment), as long as glucose levels are maintained at appropriate levels.

One of the most influential studies that emerged in the past decade – one that had a significant impact on the delivery of insulin therapy – was performed at a single center in Belgium by Van den Berghe and colleagues.⁹ Known as the Leuven protocol, this prospective, randomized, controlled study enrolled 1548 patients who were on mechanical ventilation in surgical intensive care units, and who required insulin therapy. In the control group, conventional insulin therapy was initiated only if the blood glucose level exceeded 215 mg/dL, with the intent to maintain a level between 180 and 200 mg/dL. In the experimental group, intensive insulin therapy was initiated if the blood glucose exceeded 110 mg/dL, to maintain “normoglycemia” or a glucose level of 80 to 110 mg/dL.

The results of the study demonstrated a dramatic reduction in mortality, from a rate of 8% with conventional insulin therapy to 4.6% with intensive therapy ($P<0.04$). Other important findings were attributed to intensive insulin therapy:

- A significant decrease in mortality was observed in patients who remained in the intensive care unit for more than 5 days (20.2% with conventional insulin therapy compared with 10.6% with intensive insulin therapy [$P=0.005$]).
- The greatest reduction in deaths occurred in patients who had multi-system organ failure with a sepsis focus.
- Overall in-hospital mortality was reduced by 34%.
- Bloodstream infections were reduced by 46%.
- Acute renal failure requiring dialysis or hemofiltration was reduced by 41%.

It is also important to review the NICE-SUGAR study – a large, international, randomized trial.¹⁰ This recent study included 6104 adult patients with an expected length of stay of 3 days or more in the ICU. Patients were randomly assigned to two

groups: an intensive glucose control group, with a target glucose level of 81 to 108 mg/dL, or a conventional group, with a target of 180 mg/dL or less. Findings from the NICE-SUGAR study did not uphold those of previous studies. By contrast, the results from this study showed an increase in mortality in the intensive glucose control group. At the 90-day point, mortality rates were 27.5% in the intensive glucose group and 24.9% in the conventional group ($P=0.02$). The rate of severe hypoglycemia for the two groups was also noteworthy: 6.8% in the intensive-control group compared with 0.5% in the conventional-control group ($P<0.001$).

In an editorial accompanying the NICE-SUGAR report, Inzucchi and Siegel¹² acknowledge the quandary that results from the divergent conclusions of this study and of those previous. They suggest that until further evidence becomes available, it is reasonable for clinicians to continue their attempts to optimize the management of blood glucose in hospitalized patients – especially to avert the extremes of hyperglycemia, which can acutely affect renal function, hemodynamics, and immune defenses, and hypoglycemia, which has its own, often more immediate and serious, consequences.

2009 AACE and ADA Recommendations

As a result of the inconsistent findings of the randomized controlled trials using intensive glycemic control, new clinical guidelines supporting a more moderate target of 140 to 180 mg/dL were developed. In 2009, The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) published their recommendations for glucose control.¹³ The four key recommendations for managing hyperglycemia in critically ill patients are:

- Target blood glucose level of 140 to 180 mg/dL once insulin therapy has been started
- Lower targets may be appropriate for selected patients, but targets lower than 110 mg/dL are not recommended
- IV insulin infusions are preferred
- Validated infusion protocols should be developed and implemented for efficacy, safety, and reduced variability in blood glucose levels.

While achieving and maintaining targeted blood glucose levels is the primary goal of clinical therapy, the AACE and ADA recommendations also recognize the importance of stability in blood glucose levels to further reduce complications and comorbid conditions. To achieve reduced variability in blood glucose levels, it is important to review the precipitating risk factors for hypo- or hyperglycemia. Unfortunately, many of these risk factors may be iatrogenic in origin (**Table**).

IV Insulin Infusions and Protocols

AACE and ADA recommendations name insulin infusions as the preferred method to achieve and maintain glycemic control in critically ill patients. However, insulin infusions should not be haphazardly initiated nor regulated. Clinicians should seek validated insulin infusion protocols with demonstrated efficacy and proven low rates of hypoglycemia. Likewise, frequent blood glucose monitoring must be implemented to minimize hypoglycemia and to achieve optimal glucose control.

Traditionally, insulin infusions were administered using standard, physician-guided insulin orders, which could be

evidence-based but were more a game of chance – choosing a starting point and hoping that the insulin would be sufficient to reduce the glucose level. Through the work of early researchers, paper-based, simple-calculation protocols emerged. These provided established guidelines based on regular interval glucose monitoring and a standardized approach to every infusion – standardized, but not individualized. Eventually, a combination of mathematics, physics, and medical science yielded an electronic dosing protocol. Now, clinicians have the opportunity to implement individualized insulin infusions based on the patient’s own physiological data and the modeling of response to insulin therapy.

Electronic insulin dosing programs have had a significant impact on the outcomes associated with insulin infusion therapy. Most notable is the ability to get the patient’s blood glucose level into an established target range more quickly than with paper-based or physician-ordered insulin dosing protocols. Equally important is the reduction in critical hypoglycemic events (i.e., glucose levels less than 40 mg/dL). As a result, patients are stabilized more quickly and they can transition to subcutaneous insulin earlier in their hospital stay.

Table. Hypo- and hyperglycemia: precipitating factors

- Changes in caloric or carbohydrate intake
- Changes in medications
- Failure to adjust glycemic therapy
- Prolonged use of SSI
- Poor coordination of glucose testing with insulin administration and meal delivery
- Poor communication of patient information at hand-off to different care team
- Use of long-acting sulfonylureas in elderly patients and those with kidney or liver insufficiency
- Enteral feeds, TPN, and dextrose infusions
- Errors in order writing and transcription
- Patient characteristics associated with increased risk of hypoglycemia:
 - Advanced age
 - Poor oral intake
 - Beta-blockers
 - Non-recognition of hypoglycemic symptoms

Conclusion: The CaroMont Health Experience

CaroMont Health began using an electronic dosing program in June 2009 for all adult insulin infusions, which are administered only in the critical care and step-down units. After using each of the insulin infusion methods described here, the electronic program has proven to be the most effective and efficacious for infusion management. **Figure 3** shows our recently reported outcomes associated with critical hypoglycemia and time to goal.

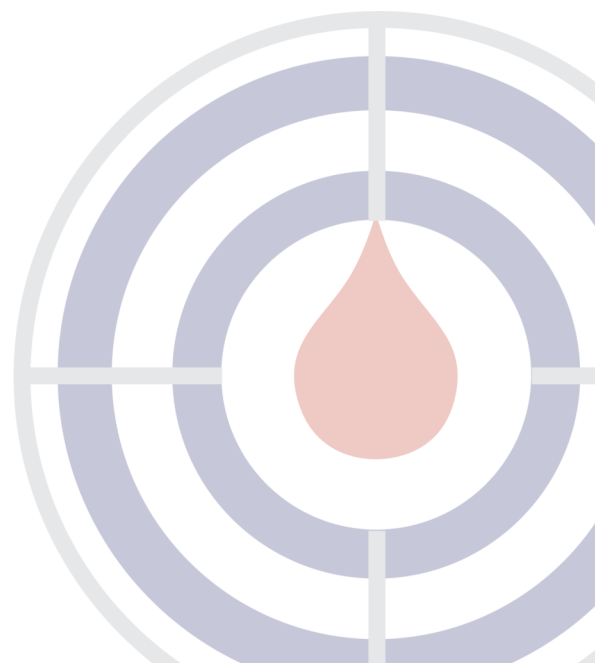
Accompanying the positive patient outcomes experienced at CaroMont Health is the support of the staff of the adult critical care units. Staff have commented on the system's ease of use, the increased patient safety they experience with electronic dosing compared with the columnar paper protocol (requiring clinician calculations), and the decreased time-to-target range that results in less-frequent finger sticks and a quicker transition to subcutaneous insulin.

Figure 3. CaroMont outcomes as of March 31, 2011

Rate of critical hypoglycemia	0.034%*
Time to goal	3.4 hours

*Before the use of electronic dosing software, rate was 0.18%.

In summary, due to multisystem failure, the majority of critically ill patients are not able to auto-regulate serum glucose levels. This predisposes them to possible hospital-acquired infections, longer hospital stay, and impaired immune response. Recognizing that their inability to regulate may be iatrogenic in origin, critical care multidisciplinary teams must recognize that individualized care and treatment modalities can decrease the mortality rates of patients who are at risk for uncontrolled hyperglycemia. Individualized care and effective communication, as well as collaborative teamwork among caregivers, will enhance the rate of survival for this patient population. Electronic dosing protocols are an added tool that can assist in individualizing insulin therapy and improving outcomes for critically ill patients.



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Post-Test

- 1. Which statement is true of critically ill patients and their ability to auto-regulate serum glucose levels?**
 - A. Critically ill patients have the same ability to regulate/use insulin as other patients
 - B. Greater than 80% of critically ill patients have demonstrated insulin resistance
 - C. Insulin administration is not effective to reduce mortality rates in the critically ill population
 - D. Critically ill patients maintain euglycemia in the same fashion as other patients
- 2. Hyperglycemia is often associated with which of the following complications in the critically ill patient?**
 - A. Delayed healing response
 - B. Impairment of the immune system
 - C. Increased risk of infection
 - D. All of the above
- 3. Which of the following factors has not been reported to affect the glycemic level of hospitalized patients?**
 - A. Oral, enteral, and parenteral intake
 - B. Immunosuppressant therapy
 - C. Antihypertensive therapy
 - D. Improper insulin dosing by clinicians
- 4. Which of the following findings was supported in the study by Umpierrez and colleagues?**
 - A. Patients with a new diagnosis of hyperglycemia were less likely to be admitted to the ICU
 - B. Newly diagnosed hyperglycemia was associated with an overall 16% mortality rate, with a significantly higher rate in ICU patients than in non-ICU patients
 - C. Patients with a history of diabetes were less likely to be admitted to the ICU
 - D. Non-ICU patients had an unexpected higher rate of newly diagnosed hyperglycemia than ICU patients
- 5. In the DIGAMI 2 study, one of the most important outcomes realized was:**
 - A. It does not matter how glucose is lowered (conventionally or with intensive insulin-based treatment), as long as glucose levels are maintained at appropriate levels
 - B. Intensive insulin-based treatment was more effective than conventional insulin therapy in reducing mortality in critically ill patients
 - C. Glucose levels were not a predictor of long-term mortality
 - D. Diabetic patients with a history of myocardial infarction had a significant reduction in mortality 1 year after intensive insulin therapy
- 6. The Leuven protocol (intensive insulin administration) demonstrated which of the following outcomes?**
 - A. Mortality reduced, from 8% with conventional insulin therapy to 4.6% with intensive therapy
 - B. Significant decrease in mortality in patients who remained in the intensive care unit for more than 5 days
 - C. Overall hospital mortality reduced by 34%
 - D. All of the above
- 7. 2009 AACE and ADA recommendations include:**
 - A. Target blood glucose level of 140 to 180 mg/dL once insulin therapy has been started
 - B. IV insulin infusions preferred
 - C. Validated infusion protocols should be developed and implemented
 - D. All of the above
- 8. Electronic insulin dosing protocols demonstrate improved efficacy over paper-based protocols. This is supported by all of the following except:**
 - A. Increase in frequency of blood glucose monitoring
 - B. The combination of math, physics, and medical science allows for individualized insulin dosing
 - C. Decrease in time to goal for targeted blood glucose levels
 - D. Decrease in critical hypoglycemic events

- 9. Which of the following is true of paper-based insulin infusion protocols?**
- A. Simple mathematical calculations are required and may result in error
 - B. Time to goal for targeted blood sugar levels has been reduced as documented in the research cited
 - C. Protocols are individualized per patient
 - D. A reduction in hypoglycemic events is noted
- 10. CaroMont Health outcomes strongly support the use of an electronic insulin-dosing protocol. These outcomes include all of the following, except:**
- A. Reduction in time to goal for targeted glucose
 - B. Significant reduction in critical hypoglycemic events
 - C. Longer transition to subcutaneous insulin
 - D. Staff report increased clinician satisfaction and patient safety

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