

# Insulin Therapy for the Critically Ill Patient

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*The risk of mortality or significant morbidity is high among critically ill patients who are treated in the intensive care unit (ICU) for >5 days. These patients are susceptible to sepsis, excessive inflammation, critical illness polyneuropathy, and multiple organ failure, the latter often being the cause of death. Most intensive care patients, even those who did not previously suffer from diabetes, are hyperglycemic, which is presumed to reflect an adaptive development of insulin resistance. In the K.U. Leuven study it was hypothesized that hyperglycemia is not a beneficial adaptation to severe illness but rather predisposes patients to many of the typical intensive care complications—prolonged intensive care dependence and death. The effects of intensive insulin therapy to maintain normoglycemia during critical illness were studied in a large group (N = 1548) of ventilated, surgical ICU patients. An algorithm was proposed for implementing this procedure. The randomly assigned intensive insulin therapy group received insulin infusion tailored to control blood glucose (BG) levels in the range 80–110 mg/dL, whereas the conventional treatment group received insulin only when glucose levels exceeded 200 mg/dL, and in that event were maintained in a target range of 180–200 mg/dL. Intensive insulin therapy induced a 43% reduction of intensive care mortality risk (P = 0.036 after correction for interim analyses) and a 34% reduction of hospital mortality (P = 0.005). A reduced risk of severe infections by 46% (P = 0.003) was associated with a 35% reduction in prolonged (>10 d) requirement for antibiotic therapy (P <0.001). In addition, excessive inflammation was prevented. Logistic regression analysis indicated that control of BG levels, rather than insulin administration itself, likely explains the observed clinical benefits. Use of insulin infusion to maintain normoglycemia using a titration algorithm, at least in populations similar to those in the Leuven study, improves outcome. Further data are needed to establish the applicability of this strategy to other patient groups, such as those in a medical ICU and in general hospital care.*

Approximately 30% of patients in tertiary level intensive care units (ICUs) require >5 days of intensive care, and despite our best efforts, the risk of mortality among these seriously ill patients is at least 20% (1). This high risk of death has not been reduced over the past few decades despite the boom in ICU technology. Hence there is still a need to develop treatment strategies that improve the outcome of critically ill patients treated in ICUs.

Of course, many ICU patients have grave underlying conditions or have undergone severe trauma or major surgery, evidenced by their very presence in the unit, and this may to a certain extent explain the high risk of death. Nevertheless, the nature of the complications that frequently occur in these patients with time in the ICU suggests there is room for improvement. There is, for example, much interest in therapies aimed at reduc-

ing the risk of sepsis and in particular septic shock in the ICU patient (2). Septic shock is the most common cause of death in the ICU and accounts for >100,000 deaths per year in the United States alone (3). Sepsis is closely associated with a series of inflammatory and metabolic responses that in part contribute to altered host defense but also may take part in the pathogenesis of multiple organ failure, which is often the cause of death in long-stay ICU patients (2). Critical-illness polyneuropathy, an axonal degenerative type of polyneuropathy frequently occurring in septic ICU patients, and skeletal muscle wasting are common complications that prolong the need for mechanical ventilation and intensive care (4–6). The exact causes of critical-illness polyneuropathy remain unclear, but its consequences are severe.

As in many areas of medicine, management of critical illness has had its share of rising hopes and disappointments as “magic bullets” have failed to reach their targets (1,7). Indeed, many trials that have evaluated agents designed to attenuate the early inflammatory events in sepsis, including antagonists against endotoxin, tumor necrosis factor- $\alpha$  (monoclonal antibodies or soluble receptor immunoadhesins), and interleukin-1, all of which have evoked positive effects in animal models, have not shown that these agents beneficially affect patient outcomes. Likewise, anabolic interventions have failed to show a benefit and some, such as those with growth hormone, appear to evoke deleterious effects. Furthermore, therapies that have shown promise can be costly and raise questions concerning distribution of resources (8).

## GLUCOSE METABOLISM: A TARGET FOR INTERVENTION IN THE ICU

It is well established that hyperglycemia is common in critically ill patients, even if there is no history of diabetes (9). This common feature presumably reflects the development of insulin resistance at the receptor and postreceptor level, particularly in the liver, skeletal muscle, and heart. This action is presumed to be an adaptive response to life-threatening illness, ensuring an adequate supply of glucose to the brain, blood cells, and injured tissues. However, recent data indicate that the bene-

fits of this response may be outweighed by detrimental effects, particularly in the chronic phase of critical illness. Data are available linking hyperglycemia with poorer outcome after stroke and brain injury and with larger infarct size after myocardial infarction (MI) (10,11). The macrovascular effects of hyperglycemia are abundantly supported by evidence in diabetes. Although these effects are thought to occur over a rather extended time frame, prevention of excessive hyperglycemia (blood glucose [BG] below 215 mg/dL) in the acute phase after MI was associated with a significant improvement of survival in MI patients with diabetes, as shown in the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) trial (11).

As well as the apparent presumably macrovascular effects of excessive hyperglycemia, there is the possible effect at the wound site: elevated BG levels have been found to be associated with increased morbidity and mortality after burns or surgery. Although there is no clear evidence for a causal relationship, effects on a range of systems can be hypothesized, including mitochondrial metabolic pathways, endothelial function, and cardiac potassium channels (12–14). The role of hyperglycemia in promoting bacterial infections of

### KEY POINT

**Hyperglycemia is common in critically ill patients even if there is no history of diabetes. The most compelling conclusion from the Leuven study is that maintaining glucose levels in the normoglycemic range is key to reducing mortality and morbidity.**

wound tissues and in the blood is also intuitive. Some of the beneficial effects of interventions that use insulin in patients with acute MI may reflect independent actions of insulin rather than normalization of hyperglycemia *per se* (12). Glucose-insulin-potassium (GIK) infusion has been shown to salvage myocardium, increase heart function,

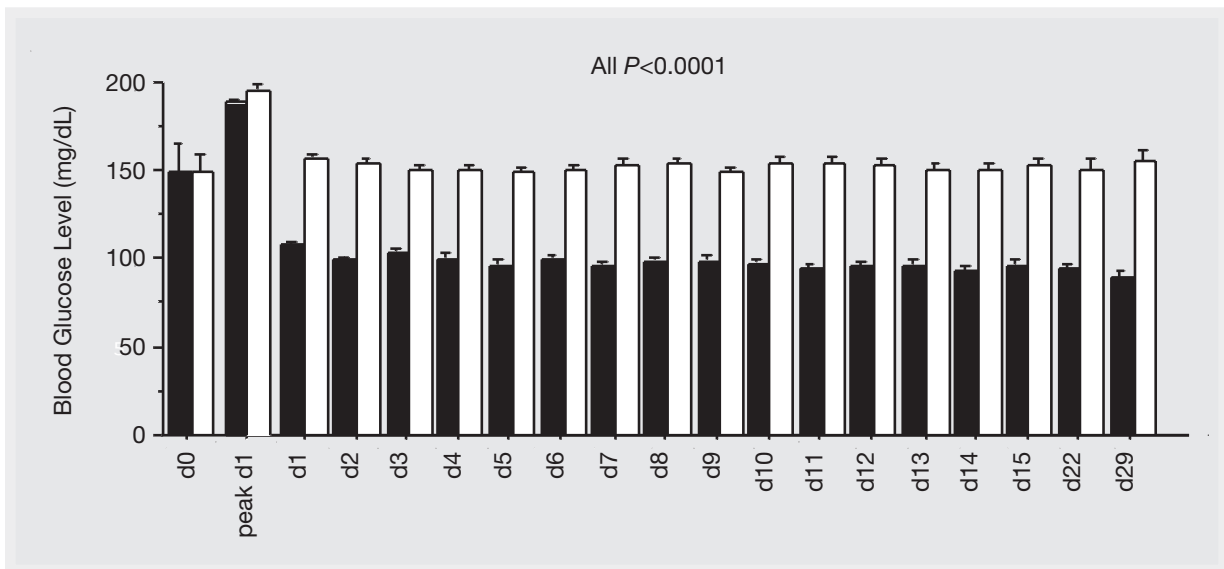
and improve mortality in patients with MI, perhaps independently of BG control (15,16). It should be noted, however, that the studied GIK infusions usually contained large amounts of insulin (0.1-1 IU/kg/h) and glucose (30 to 80 g/h) and were always infused without targeting normoglycemia. The primary goal of using GIK solutions was to forcefully stimulate myocardial metabolism of glucose instead of fatty acids when oxygen supply is compromised.

### THE K.U. LEUVEN STUDY: STRICT BG CONTROL IN CRITICALLY ILL PATIENTS WITH INTENSIVE INSULIN THERAPY

The team of ICU doctors and nurses at Leuven University Hospital investigated the impact of insulin therapy specifically directed at establishing strict normoglycemia (80 to 110 mg/dL) in a large group of 1548 patients entering the (predominantly) surgical ICU (17). All patients admitted to the unit and receiving mechanical ventilation were eligible for entry; only 14 patients were excluded (moribund status, do-not-resuscitate order in place; participation in other trial). The largest fraction (63%) of the total patient population in the study had

undergone cardiac surgery, with the remaining patients admitted for a range of noncardiac indications. The long-stay (>5 days in ICU) patient population, however, comprised a mixed patient group of whom <30% were admitted after cardiac surgery.

Patients were randomized to receive intensive (n = 765) or conventional (n = 783) therapy on entry to the ICU. Glucose levels were measured at 1- to 4-hour intervals in undiluted arterial blood. Conventionally treated patients received a continuous insulin infusion only if their BG level exceeded 215 mg/dL. Patients in the conventional group receiving insulin infusion were to be maintained in a target range of 180 to 200 mg/dL. When BG fell below that level, insulin therapy was tapered and eventually stopped. In contrast, patients in the intensive treatment group received insulin infusion as soon as BG exceeded 110 mg/dL, the infusion then being adjusted to maintain normoglycemia (80 to 110 mg/dL) (**Figure 1**). All patients were fed continuously with ~9 g of intravenous glucose per hour on admission day, followed by parenteral and/or enteral feeding according to a standard schedule and progressively increasing the caloric intake up to an average of 25 Cal/kgBW/day after 7 days. On discharge from the ICU, for logistic rea-



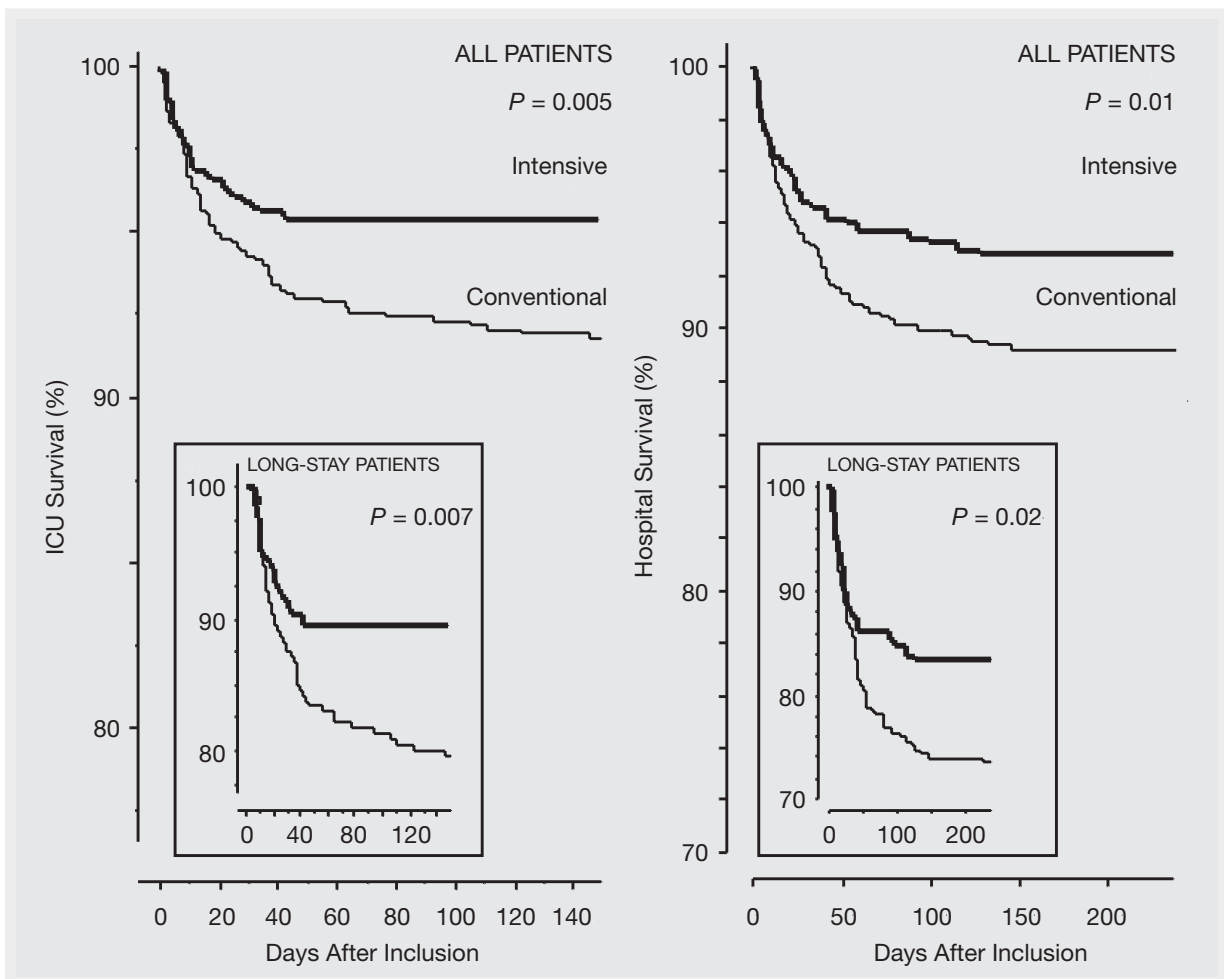
**Figure 1.** Control of blood glucose levels during the study. Data are means  $\pm$  SEM. The 0 timepoint is the blood glucose level on admission and the 1' timepoint is the peak level during the first 24 hours of intensive care on which insulin infusion was based. Based on data presented in Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med. 2003;31:359-366.

sons mainly, conventional BG control management was adopted for all patients with a target range of 180 to 200 mg/dL. Data from the 1548 patients in the study indicate that the algorithms for glucose control were appropriately applied. The conventional treatment group recorded a mean morning BG level of 153 mg/dL (being the average level of 39% insulin treated and 61% noninsulin treated patients), and the intensive group recorded 103 mg/dL ( $P < 0.0001$ ), in which virtually every patient (99%) received exogenous insulin. Caloric intake and route of feeding were similar in the 2 groups, while insulin dose was, as expected, significantly higher in the intensive group.

The primary outcome measure of the study

was in-ICU mortality, with in-hospital mortality as a secondary endpoint. Other secondary outcomes included morbidity measures such as blood stream infections.

The Leuven study was planned to continue for ~2 years; however, interim safety analyses were performed, and after 1 year, a significant reduction of in-ICU mortality was observed in the intensive treatment group, leading to the termination of the study on ethical grounds (**Figure 2**). During the study period, the mortality rate in the intensive treatment group was 4.6% versus 8.0% in the conventional group, representing a significant risk reduction of 43% ( $P = 0.036$  after adjustment for the interim analyses). The mortality reduction was



**Figure 2.** Kaplan-Meier cumulative survival curves for patients in the intensive and conventional treatment groups: survival in the intensive care unit (ICU) and survival in the hospital.  $P$  values are unadjusted. Based on data presented in Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359–1367. Reprinted with permission. © 2001, Massachusetts Medical Society. All rights reserved.

especially evident among long-stay ICU patients (intensive treatment, 10.6%; conventional treatment, 20.2%;  $P = 0.005$ ). Indeed, mortality during the first 5 days of ICU stay was not different between treatment groups. Since the group of patients in ICU >5 days comprised a minority of cardiac patients, this indicates that intensive insulin therapy to maintain strict normoglycemia exerts beneficial effects in all types of surgical ICU patients, not merely in those suffering from coronary insults or after coronary bypass surgery. The mortality benefit also was uniformly present for all strata of severity of illness on ICU admission.

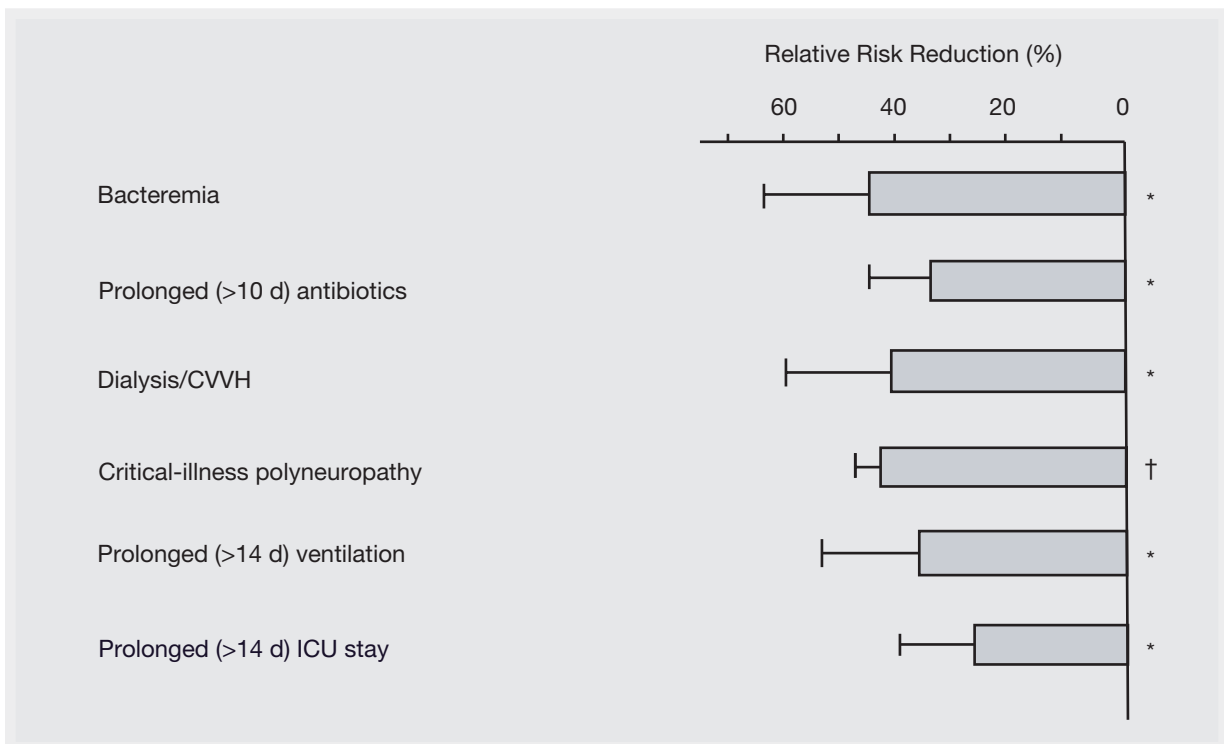
The principal cause of death among patients in both groups was multiple organ failure (intensive group, 22/35 deaths; conventional group, 51/63 deaths). However, there was an evident reduction in the intensive treatment group of the number of multiple organ failure deaths with an autopsy-proven septic focus (8 versus 33 deaths,  $P = 0.02$ ).

Morbidity analysis further showed that intensive treatment had reduced the risk of bacteremia by 46% ( $P = 0.003$ ), reflected also in a 35% reduc-

tion in risk of >10 days' antibiotic treatment ( $P < 0.001$ ). This was accompanied by a significant reduction in the duration of ventilatory support and ICU stay, a substantial reduction in the need for blood transfusions, and the presence of prolonged, excessive inflammation. Even more striking, intensive insulin therapy caused a highly significant decrease in the development and duration of critical illness polyneuropathy and acute renal failure (**Figure 3**).

### INSULIN OR GLUCOSE?

The Leuven study clearly showed that maintaining normoglycemia with an insulin infusion dramatically reduces the risk of mortality in the ICU. But, is the avoidance of hyperglycemia, or rather the provision of more insulin, the critical factor? We performed a multivariate logistic regression analysis on the effect of insulin dose and BG level on the risk of ICU mortality, corrected for all other univariate predictors of death (18,19). This indicated that both daily insulin dose and mean BG level were independent *positive* predictors of mortality.



**Figure 3.** Relative risk reductions for key measures of intensive care unit (ICU) morbidity. CVVH = continuous venovenous hemofiltration. \* $P < 0.01$ ; † $P < 0.0001$ . Based on data presented in Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359–1367.

Thus, a high glucose level increased the risk of death; meanwhile, a high daily insulin dose was also independently associated with risk of death. This strongly suggests that the lowering of the BG level or an alteration in metabolism monitored by the effect on BG levels, but not the additional

### KEY POINT

**Any algorithm for achieving and maintaining normoglycemia in the ICU can only be a recommendation and must be adapted to the individual condition of each patient. Insulin dosing should be conducted with a degree of common sense.**

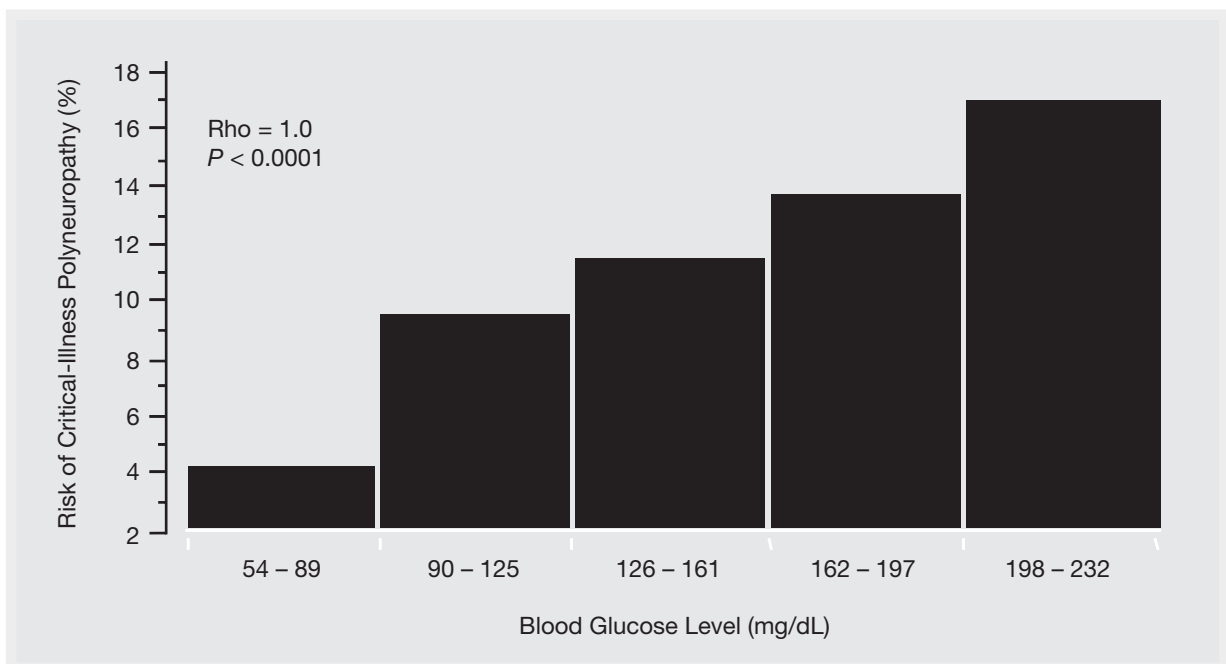
insulin given *per se*, plays the critical role. The association of insulin dose with mortality risk does not, of course, imply that insulin is itself hazardous, but likely reflects the severity of insulin resistance in the sickest individuals requiring higher insulin doses.

Further analysis of glucose levels and mor-

tality risk indicated that among long-stay ICU patients, those with better levels of glycemic control have a better prognosis, and vice versa, with no evident threshold for risk reduction above the normoglycemic range (**Figure 4**) (18). Similarly, the risk of critical-illness polyneuropathy was continuously and linearly related to BG level. Although suggestions have been made that insulin has anti-inflammatory effects, including an ability to suppress an impressive range of pro-inflammatory molecules (20), the most compelling conclusion from the Leuven study is that maintaining glucose levels in the normoglycemic range is key to reducing ICU mortality and morbidity.

### HOW TO ACHIEVE TIGHT BG CONTROL IN THE ICU

It is possible to develop an algorithm (19) for achieving and maintaining normoglycemia in the ICU (**Table**). This algorithm alone does not guarantee improvement in quality of care or clinical outcome (21). However, in the context of the treating physician's knowledge and experience, this approach could realize significant reductions in ICU mortality and morbidity.



**Figure 4.** Risk of critical-illness polyneuropathy versus blood glucose level. Based on data presented in Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359-1367.

It must be stressed, however, that insulin requirements in individual patients vary widely, depending on, for example, insulin production reserves, insulin sensitivity before and during critical illness, caloric intake in the ICU, and the severity and nature of the illness. The presence of infections or complications further affects insulin demand as does the administration of concomitant medications such as corticosteroids. As a result, any algorithm can only be a recommendation and must be adapted to the individual condition of each patient, and insulin dosing should be conducted with a degree of common sense. Also, insulin dose adjustments should be proportionate to previously observed changes in BG levels, with the dose increment becoming smaller as the patient approaches the normoglycemic range.

Even after normoglycemia is achieved, the need for monitoring of glucose levels and adjustment of insulin dose remains. In part, this anticipates an improvement in insulin sensitivity with time—necessitating a reduction in insulin dose—but also acknowledges that worsening infection, with increase in body temperature, increases insulin requirements.

Special measures are necessary for patients at risk of acute renal failure. Hourly substitution of urinary fluid loss is routinely performed in such patients to avoid fluctuations in intravascular filling status. In such cases, if the patient is receiving an insulin infusion, the substitution solutions should also contain insulin appropriate to the glucose content, additional to the insulin infusion.

For all ICU patients, reduction or interruption of caloric intake should be accompanied by reduction or interruption of insulin delivery; eg, if a patient is to be transported for investigation or surgery, all intravenous and enteral feeding is usually stopped to simplify the potentially hazardous procedure. Insulin administration should therefore also be stopped, with glucose levels being checked before transport. A patient on full enteral tube feeding may have regular daily or twice-daily interruptions of feeding to determine gastric residue, in which case insulin should also be stopped or reduced to a low (0.5 IU/h) maintenance dose during that time. When a patient is extubated prior to starting oral food intake, insulin dose will usually need to be reduced to match nutrient intake.

When a patient is ready for discharge to a

<b>TABLE.</b>		<b>SUGGESTED ALGORITHM FOR ACHIEVING AND MAINTAINING NORMOGLYCEMIA IN THE ICU</b>
<i>Test</i>	<i>Result of BG Measurement</i>	<i>Action</i>
<b>Measure BG on admission to intensive care unit</b>	>220 mg/dL 220–110 mg/dL 110 mg/dL	Start insulin 2–4 IU/h Start insulin 1–2 IU/h Don't start insulin but continue BG monitoring every 4h
<b>Measure BG every 1 to 2 h until in normal range</b>	>140 mg/dL 110–140 mg/dL Approaching normal range	Increase insulin dose by 1–2 IU/h Increase insulin dose by 0.5–1 IU/h Adjust insulin dose by 0.1–0.5 IU/h
<b>Measure BG every 4 h</b>	Approaching normal range Normal Falling steeply 60–80 mg/dL 40–60 mg/dL  <40 mg/dL	Adjust insulin dose by 0.1–0.5 IU/h Insulin dose unchanged Reduce insulin dose by half and check more frequently Reduce insulin dose and check BG within 1 h Stop insulin infusion, assure adequate baseline glucose intake, and check BG within 1 h Stop insulin infusion, assure adequate baseline glucose intake, administer glucose per 10 g IV boluses, and check BG within 1 h

Blood glucose (BG) levels are to be determined on site in undiluted arterial blood; insulin, typically 50 IU soluble human insulin in 50 mL 0.9% saline, is administered by continuous infusion through a central venous line. This algorithm is designed for use in patients receiving enteral and/or parenteral feeding. The numerical instructions provided are a guide; insulin dosage should always be done with common sense, proportionate to the previous changes in BG observed on previous changes in dosage. Based on data presented in Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med.* 2003;31:359–366.

regular ward and remains near-normoglycemic (200 mg/dL or less) when insulin is tapered to low doses (2 IU/h or less), insulin infusion could be stopped. However, if significant insulin doses are needed to maintain glucose levels below 200 mg/dL, it is likely that the patient has preexisting diabetes, and thorough follow-up by an endocrinologist should be planned. An insulin regimen should be arranged with the consulting physician to ensure appropriate follow-up. This is particularly true for surgical wards where the nursing staff often does not manage diabetic patients.

## CONCLUSIONS

Significant improvement in clinical outcome has been shown by tightening glycemic control in surgical ICU patients. Unresolved questions include the degree to which these data can be applied to other patient groups (eg, medical ICU patients, children in the ICU, surgical patients in regular wards). It also remains to be established whether hyperglycemia *per se* or rather other concomitant effects of insulin monitored by the level of BG, or a combination is responsible for the major benefits seen in the Leuven study.

## ACKNOWLEDGMENT

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## REFERENCES

1. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*. 1999;341:785–792.
2. Vincent J-L. Microvascular endothelial dysfunction: A renewed appreciation of sepsis pathophysiology. *Crit Care*. 2002;5:S1–S5.
3. Parrillo JE. Pathogenetic mechanisms of septic shock. *N Engl J Med*. 1993;328:1471–1478.
4. Zochodne DE, Bolton CF, Wells GA, et al. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. *Brain*. 1987;110:819–841.
5. Leijten FSS, de Weerd AW. Critical illness polyneuropathy: A review of the literature, definition and pathophysiology. *Clin Neurol Neurosurg*. 1994;96:10–19.
6. Bolton CF. Sepsis and the systemic inflammatory response syndrome: Neuromuscular manifestations. *Crit Care Med*. 1996;24:1408–1416.
7. Venn R. Sepsis, insulin and noninvasive ventilation. *Crit Care*. 2002;6:93–94.
8. Hawryluck L, Crippen D. Ethics and critical care in the new millennium. *Crit Care*. 2002;6:1–2.
9. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. *Best Pract Res Clin Endocrinol Metab*. 2001;15:533–551.
10. Kagansky N, Levy S, Knobler H. The role of hyperglycemia in acute stroke. *Arch Neurol*. 2001;58:1209–1212.
11. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. *Lancet*. 2000;355:773–778.
12. Groeneveld ABJ, Beishuizen A, Visser FC. Insulin: A wonder drug in the critically ill? *Crit Care*. 2002;6:102–105.
13. Gore DC, Chinkes D, Hegggers J, et al. Association of hyperglycemia with increased mortality after severe burn injury. *J Trauma*. 2001;51:540–544.
14. Ljungqvist O, Nygren J, Thorell A. Insulin resistance and elective surgery. *Surgery*. 2000;128:757–760.
15. Diaz R, Paolasso EC, Piegas LS, et al, on behalf of the ECLA (Estudios Cardiológicos Latinoamerica) Collaborative Group. Metabolic modulation of acute myocardial infarction: The ECLA Glucose-Insulin-Potassium Pilot Trial. *Circulation*. 1998;98:2227–2234.
16. Jonassen AK, Sack MN, Mjøs OD, et al. Myocardial protection by insulin at reperfusion requires early administration and is mediated via Akt and p70s6 kinase cell-survival signaling. *Circ Res*. 2001;89:1191–1198.
17. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
18. Van den Berghe G, Bouillon R, Lauwers P. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2002;346:1587–1588.
19. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med*. 2003;31:359–366.
20. Das UN. Insulin and the critically ill. *Crit Care*. 2002;6:262–263.
21. Wall RJ, Dittus RS, Ely EW. Protocol-driven care in the intensive care unit: A tool for quality. *Crit Care*. 2001;5:283–285.