

THERAPEUTICS

# Intensive insulin therapy reduced mortality and morbidity in critically ill patients

Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001 Nov 8;345:1359-67.

**QUESTION**

In patients who are critically ill, does normalization of blood glucose levels with intensive insulin therapy reduce mortality and morbidity?

**DESIGN**

Randomized (allocation concealed\*), blinded (patients and outcome assessors),\* controlled trial with {mean follow-up of 23 days}†.

**SETTING**

Surgical intensive care unit (ICU) at a university hospital in Leuven, Belgium.

**PATIENTS**

1548 patients (mean age 63 y, 71% men) admitted to the ICU who were receiving mechanical ventilation. Patients were excluded if they were participating in another trial, were moribund, or had do-not-resuscitate orders. Follow-up was 100%.

**INTERVENTION**

Patients were assigned to intensive ( $n = 765$ ) or conventional ( $n = 783$ ) insulin therapy. Intensive therapy was insulin infusion that was begun if the blood glucose level was  $> 6.1$  mmol/L and adjusted to maintain normoglycemia (maximum insulin dose 50 IU/h). Conventional therapy was continuous insulin infusion by a pump that was begun if the blood glucose level was  $> 11.9$  mmol/L and adjusted to maintain a blood glucose level between 10.0 and 11.1 mmol/L. All

patients were given continuous intravenous glucose on ICU admission, and total enteral feeding was attempted as early as possible.

**MAIN OUTCOME MEASURES**

The primary outcome measure was all-cause mortality in the ICU. Secondary outcome measures included in-hospital mortality, duration of ICU stay, need for ICU care or ventilatory support for  $> 14$  days, and various diseases.

**MAIN RESULTS**

Analysis was by intention to treat. Patients who received intensive insulin therapy had reduced rates of all-cause ICU mortality ( $P < 0.04$ ), in-hospital mortality ( $P = 0.01$ ), ICU care  $> 14$  days ( $P = 0.01$ ), ventilatory support  $> 14$  days ( $P = 0.003$ ), renal failure requiring dialysis or hemofiltration

( $P = 0.007$ ), bloodstream infections in the ICU ( $P = 0.003$ ), and critical-illness polyneuropathy ( $P < 0.001$ ) (Table). The groups did not differ for duration of ICU stay (median 3 d in both groups,  $P = 0.2$ ).

**CONCLUSION**

In patients who are critically ill, normalization of blood glucose levels with intensive insulin therapy reduced mortality and morbidity.

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*For correspondence: Dr. G. Van den Berghe, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium. E-mail greta.vandenbergh@med.kuleuven.ac.be.*

\*See Glossary.

†Information provided by author.

**Intensive vs conventional insulin therapy in critically ill patients‡**

Outcomes at mean 23 d	Intensive	Conventional	RRR (95% CI)	NNT (CI)
All ICU mortality	5%	8%	43% (15 to 62)	29 (17 to 94)
All in-hospital mortality	7%	11%	34% (9 to 52)	27 (15 to 122)
ICU stay $> 14$ d	11%	16%	28% (7 to 44)	23 (13 to 108)
Ventilatory support $> 14$ d	8%	12%	37% (14 to 54)	23 (14 to 67)
Renal failure requiring dialysis or hemofiltration	5%	8%	41% (13 to 60)	30 (17 to 112)
Bloodstream infection	4%	8%	46% (19 to 65)	28 (17 to 79)
Critical-illness polyneuropathy	29%	52%	45% (28 to 59)	4 (3 to 8)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data provided by author.

**COMMENTARY**

In the study by Van den Berghe and colleagues, in patients on mechanical ventilation and having a prolonged ICU stay, those who received intensive insulin therapy had lower mortality than did those who received conventional insulin therapy regardless of glucose level at admission. This is the second large trial reporting improved outcomes in hospitalized patients with hyperglycemia. The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (1) reported improved outcomes in diabetic patients who received aggressive insulin therapy after myocardial infarction; however, only 13% of patients in the present study had diagnosed diabetes.

Patients with multiorgan failure with sepsis had the greatest reduction in mortality. Investigators have long recognized that leukocyte and complement function are impaired during hyperglycemia, hyperglycemia is associated with increased infection rates, and in vitro glucose control leads to improved leukocyte function (2). Surprisingly, increased morbidity and mortality were seen when the mean morning glucose level in

the conventional insulin-therapy group was 8.5 mmol/L (traditionally regarded as reasonable for hospitalized patients during parenteral or enteral feeding).

To safely translate this study to clinical practice will require a system redesign, including mandatory insulin-infusion algorithms and dedicated support services to achieve target glucose levels while minimizing hypoglycemia. Further studies are needed to determine the degree of glucose control required to achieve similar benefits in other patient groups and to determine optimal implementation strategies in the ICU.

*Daniel L. Hurley, MD  
M. Molly McMahon, MD  
Mayo Clinic  
Rochester, Minnesota, USA*

**References**

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