Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients*

Greet Van den Berghe, MD, PhD; Pieter J. Wouters, MSc; Katrien Kesteloot, PhD; Daniel E. Hilleman, PharmD

LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Describe intensive insulin therapy.
2. Identify the costs of conventional and intensive insulin therapy.
3. Use this information in a clinical setting.

Dr. Van den Berghe has disclosed that he is the recipient of direct grant/research funds from Lifescan. Dr. Hilleman has disclosed that he is/was on the speaker's bureau of Life Scan, Roche, Pfizer, and Abbott. Mr. Wouters and Dr. Kesteloot have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity. The authors have disclosed that the use of insulin has not been approved by the FDA as discussed in this article.

Wolters Kluwer Health had identified and resolved all faculty conflicts of interest regarding this educational activity.

Visit the *Critical Care Medicine* Web site (www.ccmjournal.org) for information on obtaining continuing medical education credit.

Objective: **To perform an analysis of healthcare resource utilization with intensive insulin therapy, which has recently been shown to reduce morbidity and mortality rates of mechanically ventilated critically ill patients in a surgical intensive care unit.**

Design: **A *post hoc* cost analysis.**

Setting: **Surgical intensive care unit.**

Patients: **Patients were 1548 mechanically ventilated patients admitted to a surgical intensive care unit.**

Interventions: **A *post hoc* cost analysis was conducted based on data collected prospectively as part of a large randomized controlled trial. The analysis performed was a healthcare resource utilization analysis in which the cost of hospitalization in the intensive care unit was determined based on length of stay and the frequency of crucial cost-generating morbid events occurring in the intensive and conventional insulin treatment groups. Sensitivity analyses were performed to evaluate the robustness of the findings. Discounting of costs was not performed as treatment was limited to the intensive care stay and follow-up was not continued beyond hospitalization.**

Measurements and Main Results: **In the intensive treatment group, total treatment cost was 109,838 Euros (144 Euros per patient). In the conventional treatment group, total treatment cost was 56,359 Euros (72 Euros per patient). The excess cost of intensive insulin therapy was 72 Euros per patient. The total hospitalization cost in the intensive treatment group was 6,067,237 Euros (7931 Euros per patient) compared with 8,275,394 Euros (10,569 Euros per patient) in the conventional treatment group. The excess cost of intensive care unit hospitalization in the conventional vs. intensive treatment group was 2638 Euros per patient. These intensive care unit benefits were not offset by additional costs for care on regular wards.**

Conclusions: **Intensive insulin therapy, which reduces morbidity and mortality rates of mechanically ventilated patients admitted to a surgical intensive care unit, is associated with substantial cost savings compared with conventional insulin therapy. (Crit Care Med 2006; 34:●●●–●●●)**

Hyperglycemia and insulin resistance are common findings in critically ill patients, even those without diabetes mellitus (1–3). Elevated blood glucose levels, even a single value obtained at the time of hospital admission, has been associated with adverse outcomes in a variety of clinical settings (4–8). Hyperglycemia during hospitalization was also found to be an independent predictor of adverse outcomes in patients admitted with stroke (9). Until recently, it was unclear whether this association merely reflects the severity of the primary injury or rather that hyperglyce-

*See also p. 000.

Professor of Medicine, Head, Department of Critical Care, University of Leuven, Leuven, Belgium (GVdB); Research Officer, Department of Intensive Care Medicine, UZ Leuven—University of Leuven, Leuven, Belgium (PJW); Full Professor, K. U.K. U. Leuven, CFO, University Hospitals Leuven, Leuven, Belgium (KK); Professor of Pharmacy, Creighton University School of Pharmacy, Omaha, NE (DEH).

Supported, in part, by the Fund for Scientific Research, Flanders, Belgium (G.0278.03), the Research Council of the Catholic University of Leuven (OT 03/56), the Belgian Foundation for Research in Congenital Heart Diseases, and a research grant from Lifescan. Greet Van den Berghe is a Fundamental Clinical Research Investigator (G.3C05.95N) for the Fund for Scientific Research, Flanders, Belgium, and holds an unrestricted Catholic University of Leuven Novo Nordisk Chair of Research.

DOI: 10.1097/01.CCM.0000201408.15502.24

mia acts as a secondary insult which is contributing to worse outcomes.

In a randomized controlled trial in mechanically ventilated patients admitted to a surgical intensive care unit (ICU) (further referred to as the "Leuven study"), strict normalization of blood glucose (80–110 mg/dL) with insulin during the time a patient is treated in the ICU significantly reduced morbidity and mortality rates compared with a conventional approach in which insulin was given only when the blood glucose level exceeded 215 mg/dL (10). The occurrence of acute renal failure, critical illness polyneuropathy, transfusion requirements, sepsis, and ventilator and intensive care dependency were also significantly reduced by intensive insulin therapy. It is important to note that only 13% of the patients enrolled in this study were diabetic. These results have recently led to the publication of a position statement regarding more aggressive blood glucose targets for hospitalized patients (11).

When a treatment strategy is recommended for use in a large patient population, it is important to evaluate the costs of that treatment strategy. The purpose of the current study was to perform a healthcare resource utilization analysis of intensive insulin therapy in mechanically ventilated intensive care patients based on prospectively collected data from the Leuven study.

METHODS

Study Design. The methods and major clinical findings of the Leuven study have been previously reported (10). In brief, 1548 mechanically ventilated patients admitted to a surgical ICU were randomized to receive intensive insulin therapy or conventional insulin therapy. Informed consent had been obtained from the closest family member before inclusion, and the ethical review board of the Leuven University School of Medicine had approved the protocol. The two patient groups were comparable at inclusion, both for severity of illness and for preexisting comorbidities (10). In the intensive insulin therapy group, a continuous insulin infusion was initiated if the blood glucose exceeded 110 mg/dL and was titrated to maintain blood glucose at a level between 80 and 110 mg/dL. The mean ± SD level of blood glucose control in the intensive insulin group was 103 ± 19 mg/dL. In the conventional insulin therapy group, a continuous insulin infusion was initiated only when the blood glucose exceeded 215 mg/dL and then was titrated to maintain blood glucose at a level between 180 and 200 mg/dL. The infusion was tapered and stopped if blood glucose levels fell below that threshold. The mean ± SD level of blood glucose control in the conventional group was 153 ± 33 mg/dL. Following discharge from the ICU, the conventional treatment approach was used in all patients.

Insulin was administered by continuous infusion through a central venous catheter in both groups of patients. Insulin dose was adjusted by the clinical nursing staff of the ICU according to whole blood glucose levels determined at the bedside and following dosing guidelines. Blood glucose levels were determined every 1–2 hrs during the first 12–24 hrs after initiation of insulin until stabilization of the blood glucose level at the set target and every 4 hrs thereafter. Patients not receiving insulin infusions had blood glucose determinations at 4-hr intervals during their ICU stay. All patients received partial nutritional support (8 g/hr intravenous glucose) during the first day of intensive care stay and progressively increasing amounts of standardized enteral and/or parenteral feedings thereafter, with enteral feeding attempted as early as possible. Patients were followed throughout hospital stay.

The effects of the intervention on the studied cost-generating morbidity items, as previously reported (10), are given in Table 1.

Healthcare Resource Utilization Analysis and Statistical Analysis. Costs were determined for the following healthcare resources: duration of mechanical ventilation, days in the ICU, days on hemodialysis/hemofiltration, duration of therapy with certain drugs (vasopressors, inotropes, and antibiotics), blood transfusions, insulin administration, and blood glucose monitoring. These specific cost items were the ones that were affected by the intervention, either directly or indirectly by the impact on stay in ICU. To determine eventual impact on costs for care on general wards, we calculated days spent on the wards for both survivors and nonsurvivors in both study groups, and we assessed need for hemodialysis on the regular wards. Total healthcare costs were determined by multiplying the frequency of use of each healthcare resource in the respective treatment group by its cost. These calculations were done on a per-patient basis. Costs were presented as the median and interquartile range.

The cost of insulin administration and blood glucose monitoring included the following: units of regular insulin, 0.9% sodium chloride for injection, intravenous infusion pump, intravenous tubing, and whole blood glucose determinations (point of care) (Table 2). Costs for these items were based on wholesale acquisition cost at the Leuven University Hospital. For patients not receiving insulin infusions, only the costs of systematic blood glucose monitoring were included. For the intensive insulin group, the higher frequency of monitoring during the first 24 hrs compared with the other days in ICU was taken into account in the calculation.

Costs for ICU length of stay, mechanical ventilation, and dialysis were determined using "top-down" accounting methods. In this method, actual costs of personnel, materials used, and depreciation are allocated directly to the cost centers where the resources were deployed. Overhead costs were allocated across cost centers on the basis of allocation criteria. The most important allocation keys were the number of full-time equivalents and materials. Based on these data, the costs of a 1-day stay in an intensive care unit were calculated based on the total direct cost allocated to the ICU plus indirect costs, allocated to the same ICU, divided by the actual number of stay days on the same unit. In the ICU stay calculation, the direct costs specific for dialysis and mechanical ventilation were excluded. These costs were used to calculate a daily cost per dialysis session or mechanical ventilation over and above the ICU stay.

The cost of medications (vasopressors, inotropic agents, antibiotics, and also insulin) and blood transfusions was based on the actual types and amounts of medication/blood products used by the patients, including the costs for the drugs, the solutes, the tubings, and the infusion pumps. To calculate the per-day cost of infusion pumps, we took into account purchase price, use of the pump in years, cost per year (annuity), and the number of days the pump is used bedside per year. The cost basis for these products was the wholesale acquisition cost to the hospital.

The incidence of a brief hypoglycemia increased from 0.8% to 5.2% but was never associated with clinically detectable, relevant consequences (10). Treatment for hypoglycemia only required administration of a bolus of glucose (per 10 g) and additional measurements of the level of blood glucose. Additional costs for this intervention were negligible.

Since staffing conditions were not altered to implement intensive insulin therapy, it was not necessary to attribute staffing costs to the intervention group.

Because the data for both hospitalization resource utilization and cost and were not normally distributed, nonparametric Mann-Whitney U tests were used to compare median costs. The *a priori* level of statistical significance was $p < .05$. No corrections for multiple comparisons were made.

RESULTS

Costs of insulin therapy and blood glucose monitoring are shown in Table 3. The insulin dose and volume of solution administered in the intensive treatment group were greater than in the conventional treatment group, resulting in a greater cost for insulin administration (14.05 Euros/day vs. 11.71 Euros/day). Blood glucose monitoring was more frequent during the first 24 hrs of insulin therapy resulting in a

Table 1. Effect of intensive insulin therapy on the studied cost-generating items

Variable	Conventional (n = 783)	Intensive (n = 765)	*p* Value
Days on ventilatory support	7.1 ± 0.5	5.2 ± 0.4	.004
Days in intensive care	8.6 ± 0.5	6.6 ± 0.4	.005
Days on a regular ward	14.8 ± 0.7	15.9 ± 0.9	.4
Inotropes			
No. of patients requiring inotropes	529 (67.6%)	516 (67.5%)	.9
No. of days on inotropes	2.8 ± 0.2	2.3 ± 0.1	.06
Vasopressors			
No. of patients requiring vasopressors	311 (39.7%)	292 (38.2%)	.5
No. of days on vasopressors	2.9 ± 0.3	1.9 ± 0.1	.002
Dialysis			
Dialysis during intensive care			
No. of patients requiring dialysis	64 (8.2%)	37 (4.8%)	.008
No. of days on dialysis	1.2 ± 0.2	0.0 ± 0.0	.004
Dialysis on the regular wards			
No. of patients requiring dialysis on wards	11 (1.4%)	12 (1.6%)	.8
Antibiotics			
No. of patients requiring antibiotics	757 (96.7%)	742 (97.0%)	.7
No. of days on antibiotics	6.2 ± 0.4	4.4 ± 0.3	.0002
Red cell transfusions			
No. of patients requiring transfusion	243 (31.0%)	219 (28.6%)	.3
No. of days transfused	1.0 ± 0.01	0.6 ± 0.06	.001
Insulin			
No. of patients requiring insulin	307 (39.2%)	755 (98.7%)	<.0001
No. of days on insulin	2.2 ± 0.3	6.5 ± 0.4	<.0001

Data are represented as absolute numbers (percentages) and as mean ± SEM. *p* values were obtained by Chi-square or unpaired Student's *t*-test or Mann-Whitney *U*-test, when appropriate. These data are calculated from a study that was published previously (10).

Table 2. Health care resource costs used in the study

Variable	Cost, €
Intensive care unit stay (per day)	1030.00
Mechanical ventilation (per day)	40.80
Hemodialysis (per day)	386.00
Intravenous tubing (changed every day)	4.77
Intravenous infusion pump (per day)	4.75
0.9% sodium chloride for injection (50 mL)	1.20
Regular human insulin (per unit)	0.03
Whole blood glucose determination	0.90

higher monitoring cost on the first day of treatment compared with subsequent days of treatment (16.20 Euros/day vs. 5.40 Euros/day). Patients not receiving insulin had a median blood glucose monitoring cost of 5.40 Euros/day regardless of treatment group.

Costs of insulin therapy and blood glucose monitoring in the two treatment groups are summarized in Table 4. In the intensive insulin treatment group, 755 of 765 patients received insulin therapy. All 755 of these patients received insulin therapy for their entire stay in the ICU. The mean ICU length of stay was 6.6 days in the intensive insulin treatment group. The cost of insulin infusion therapy in this group was 74,254 Euros (69,868–78,747 Euros). Blood glucose monitoring costs in the intensively treated group for patients receiving and not receiving insulin infusions were 35,225 Euros (15,819–47,184 Euros) and 359 Euros (60–538 Euros), respectively. The total treatment cost was 109,838 Euros (85,747–126,479 Euros), with an average cost per patient of 144 Euros (112–165 Euros).

In the conservative insulin treatment group, 307 patients received insulin therapy for two thirds of their ICU length of stay. The mean ICU length of stay in the conventional insulin treatment group was 8.6 days. The cost of insulin infusion therapy in this group was 21,570 Euros (20,299–22,841 Euros). Blood glucose monitoring costs in the conventionally treated group receiving and not receiving insulin infusions were 12,848 Euros (5,941–17,222 Euros) and 21,941 (3,657–32,911 Euros), respectively. The total treatment cost in the conventional treatment group was 56,359 Euros (29,897–72,974 Euros), with an average patient cost of 72 Euros (38–93 Euros). The difference in the cost of treatment between the two treatment groups was 72 Euros (19–127 Euros) ($p = .03$).

The costs of the healthcare resources in the intensive and conventional insulin treatment groups are shown in Table 5. Differences in cost of ICU stay, mechanical ventilation, dialysis, antibiotic treatment, and blood transfusions were significantly different between the treatment groups. Patients treated with intensive insulin therapy had a total treatment cost of 6,067,237 Euros (5,160,593–7,043,537 Euros) compared with 8,275,394 Euros (7,214,502–8,958,120 Euros) for patients treated with conventional insulin therapy. The per-patient cost in the intensive insulin therapy group was 7931 Euros (6746–9031 Euros) compared with 10,569 Euros (9214–11,441 Euros) for patients in the conventional insulin therapy group. This represents cost savings of 2638 Euros (183–4695 Euros) per patient.

The cost savings in ICU observed for the intensive insulin treated patients were not offset by extra costs on the wards, as indicated by a similar number of days patients spent on regular wards for both groups (median [interquartile range] of 10 [6–15] days and a mean 14.8 days in the conventional group vs. a median 10 [7–16] days and a mean 15.9 days in the intensive group, $p = .4$, Table 1). Days spent on regular wards were also not different between insulin treatment groups, considering survivors (a median 10 [7–16] days and a mean 15.6 days in the conventional group vs. a median 10 [7–16] days and a mean 16.1 days in the intensive group; $p > .9$) and nonsurvivors (a median 15 [9–38] days and a mean 32.0 days in the conventional group vs. a median 17 [7–55] days and a mean 29.8 days in the intensive group; $p = .9$) separately. Likewise, the number of patients requiring hemodialysis while on the reg-

ular wards were similar (11 [1.4%] in the conventional group vs. 12 [1.6%] in the intensive group; $p = .8$).

DISCUSSION

Intensive insulin therapy titrated to maintain normoglycemia in mechanically ventilated critically ill patients in a single center surgical ICU has been shown to reduce morbidity and mortality rates. The current *post hoc* healthcare resource utilization analysis has shown intensive insulin therapy to be associated with a substantial reduction in hospital costs (cost savings of 2638 Euros per patient). The cost savings occurred because of reductions in ICU length of stay and several morbid events such as renal failure, sepsis, blood transfusions, and mechanical ventilation dependency. The reduction in morbid events and their associated costs more than offset the small additional cost of intensive insulin therapy and the more intensive monitoring (72 Euros per patient) associated with its use. The cost savings in the ICU were not offset by additional costs for care on regular wards. Since only part of the resource utilization was taken into account in the current study, it is likely that costs savings were underestimated.

Elevated blood glucose levels have previously been associated with an excess risk of adverse clinical events in other populations of critically ill patients (4–8). These include patients with stroke or closed-head injury, acute coronary syndromes, and cardiac surgery. The efficacy and safety of intensive insulin therapy have been evaluated in diabetic patients with acute myocardial infarction and following coronary artery bypass graft surgery (12, 13). A recent observational study of the impact of implementation of this therapy in a noninvestigational ICU setting, performed at the Stamford Hospital affiliated with the Columbia University College of Physicians and Surgeons, confirmed the outcome results of the Leuven study (14). In addition, the study conducted at the Stamford Hospital confirmed that staffing conditions were not affected by the implementation of an intensive insulin treatment strategy. This study also confirmed the absence of hypoglycemia-induced morbidity. Hence, these pharmacoeconomic results appear applicable to real-life ICU practice.

In the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, intensive insulin therapy significantly reduced mortality at 1 yr (19%) compared with controls (26%) (13). Intensive insulin therapy in this study of patients with diabetes consisted of an insulin-glucose infusion for ≥24 hrs followed by subcutaneous multiple-dose insulin for ≥3 months. Mortality rates at the 3- and 6-month follow-up periods were reported to be lower in the intensive insulin group but did not reach statistical significance. A *post hoc* economic analysis of the DIGAMI trial found intensive insulin therapy to be cost effective (16,900 Euros per life year gained) (13). It is important to note that this study included only patients with diabetes mellitus. In addition, the mortality benefit did not reach significance until 1 yr after initiation of therapy. The contribution of early intravenous insulin as opposed to the longer term control of blood-glucose is hitherto unknown.

Our economic analysis has some inherent limitations. First, the study could not be performed in a blinded fashion, inherent to the titration of insulin to blood glucose levels. Second, costs or charges were not available for the entire hospitalization. As a result, costs for significant sources of cost (comorbidities, length of stay, drugs) were identified in the *post hoc* setting. This approach may have overlooked some costs. In addition,

Table 3. Costs of insulin infusions and blood glucose determinations

Variable	Cost, €/day (range)
Insulin infusion	
Intensive group	14.05 (13.22–14.90)
Conventional group	11.71 (11.02–12.40)
Blood glucose monitoring	
Insulin infusion day 1	16.20 (10.80–21.90)
Insulin infusion day 2 and after	5.40 (1.80–7.20)
No insulin infusion	5.40 (0.90–8.10)

Table 4. Costs of insulin therapy in € (range) and blood glucose monitoring in the intensive and conventional treatment groups based on all enrolled patients

Variable	Intensive (n = 765)	Conventional (n = 783)
Insulin infusion	74,254[a] (69,868–78,747)	21,570[a] (20,299–22,841)
Blood glucose monitoring		
With insulin infusion	35,225[b] (15,819–47,194)	12,848[b] (5941–17,222)
Without insulin infusion	359[c] (60–538)	21,941[c] (3657–32,911)
Total treatment costs	109,838[d] (85,747–126,479)	56,359[d] (29,897–72,974)
Average cost per patient	144[d] (112–165)	72[d] (38–93)
Excess cost for intensive insulin therapy	72 (19–127)	

[a] $p < .001$; [b] $p < .01$; [c] $p < .0001$; [d] $p = .03$.

Table 5. Per patient costs of health care resources in € (range) consumed in the intensive and conventional treatment groups

	Costs	
Variable	Intensive Therapy (n = 765)	Conventional Therapy (n = 783)
Intensive care unit stay	6,826[a] (5774–7978)	8833[a] (7665–9992)
Mechanical ventilation	204[b] (160–250)	283[b] (238–305)
Dialysis	196[c] (172–219)	473[c] (443–503)
Inotropic support	52[d] (50–54)	70[d] (52–73)
Vasopressor support	11[d] (10–12)	17[d] (16–18)
Antibiotic treatment	270[e] (248–292)	438[e] (387–487)
Blood transfusions	228[b] (219–238)	383[b] (359–408)
Insulin administration/blood glucose monitoring	144[f] (112–165)	72[f] (38–93)
Per patient total	7931[g] (6746–9031)	10,569[g] (9214–11,441)

[a] $p = .034$; [b] $p = .04$; [c] $p = .023$; [d] nonsignificant; [e] $p = .037$; [f] $p = .03$; [g] $p < .001$.

Our economic analysis demonstrates that tight blood glucose control in the intensive care unit setting is associated with substantial reductions in overall medical care costs.

follow-up beyond hospitalization was not carried out. As a result, it was not possible to evaluate the long-term impact of this intervention. Finally, since the data were generated in a single center, they cannot be directly extrapolated to other settings.

CONCLUSIONS

Hyperglycemia during critical illness contributes to adverse outcomes, and intensive insulin therapy to maintain normoglycemia has been shown to reduce mortality rates and prevent morbidity in surgical ICU patients. Evidence is accumulating that these results are also applicable to mixed surgical-medical ICUs and to real-life ICU situations beyond the setting of randomized controlled trials. Our economic analysis demonstrates that tight blood glucose control in the ICU setting is associated with substantial reductions in overall medical care costs.

REFERENCES

1. Wolfe RR, Allsop JR, Burke JF: Glucose metabolism in man: Responses to intravenous glucose infusion. *Metabolism* 1979; 28: 210–220
2. Wolfe RR, Herndon DN, Jahoor F, et al: Effect of severe burn injury on substrate cycling by glucose and fatty acids. *N Engl J Med* 1987; 317:403–408
3. Shangraw RE, Jahoor F, Miyoshi H, et al: Differentiation between septic and postburn insulin resistance. *Metabolism* 1989; 38: 983–989
4. 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
5. Umpierrez GE, Isaacs SD, Bazargan N, et al: Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrin Metab* 2002; 87:978–982
6. Capes SE, Hunt D, Malmberg K, et al: Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systematic overview. *Stroke* 2001; 32:2426–2432
7. Foo K, Cooper J, Deaner A, et al: A single serum glucose measurement predicts adverse outcomes across the whole range of acute coronary syndromes. *Heart* 2003; 89: 512–516
8. Rovlias A, Kotsou S: The influence of hyperglycemia on neurological outcome in patients with severe head injury. *Neurosurgery* 2000; 46:335–434
9. Baird TA, Parsons MW, Phanh T, et al: Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke* 2003; 34: 2208–2214
10. 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
11. American College of Endocrinology: Position statement on inpatient diabetes and metabolic control. *Endocr Pract* 2004;10:77–82
12. Furnary AP, Gao G, Grunkemeier GL, et al: Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003; 125:1007–1021
13. Almbrand B, Johannesson M, Sjostrand B, et al: Cost-effectiveness of intense insulin treatment after acute myocardial infarction in patients with diabetes mellitus: results from the DIGAMI study. *Eur Heart J* 2000; 21: 733–739
14. Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004;79:992–1000