

REDUCTION OF NOSOCOMIAL INFECTIONS IN THE SURGICAL INTENSIVE-CARE UNIT BY STRICT GLYCEMIC CONTROL

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ABSTRACT

Objective: To investigate whether hyperglycemia in glucose-intolerant patients without diabetes could lead to increased nosocomial infections in the surgical intensive-care unit (ICU).

Methods: A prospective, randomized, controlled clinical trial was conducted in the surgical ICU of a large teaching hospital in Hartford, Connecticut. Adult patients admitted to a 12-bed surgical ICU requiring treatment of hyperglycemia (glucose values ≥ 140 mg/dL) were randomly assigned to receive standard insulin therapy (target glucose range, 180 to 220 mg/dL) or strict insulin therapy (target glucose range, 80 to 120 mg/dL) throughout their ICU stay. Demographic data, comorbidities, and confounding variables were analyzed. Outcome measures included mean daily serum glucose values, mean daily insulin doses, and number of nosocomial infections during the ICU stay.

Results: The study was completed by 61 critically ill surgical patients (27 in the standard glucose control group and 34 in the strict glucose control group). A significant reduction ($P < 0.001$) in mean daily glucose level was achieved in the strict glyceemic control group (125 ± 36 mg/dL) in comparison with the standard glyceemic control group (179 ± 61 mg/dL). Furthermore, a significant reduction ($P < 0.05$) in the incidence of total nosocomial infections, including intravascular device, bloodstream, intravascular device-related bloodstream, and surgical site infections, was observed in the strict glucose control group in comparison with the standard glucose control group. The incidence of hypoglycemia (glucose levels < 60 mg/dL) was significantly increased ($P < 0.001$) in the strict glyceemic control group in comparison with the standard glyceemic control group (32% versus 7.4% of patients or 0.8% versus 0.1% of total serum glucose values, respectively).

Conclusion: Strict glyceemic control is a safe and effective method for reducing the incidence of nosocomial infections in a predominantly nondiabetic, general surgical ICU patient population. (*Endocr Pract.* 2004; 10[Suppl 2]:46-52)

Abbreviations:

CDC = Centers for Disease Control and Prevention; ICU = intensive-care unit; IVDI = intravascular device infection

BACKGROUND

Hospital-acquired (nosocomial) infections have increased during the past decade and now represent the fourth leading cause of death in the United States. Once infections become established, antimicrobial therapy is often limited by drug toxicities and the emergence of organisms resistant to multiple drugs. Prevention of nosocomial infections would avoid the excess morbidity, mortality, and costs associated with current treatment-based algorithms. Furthermore, there is the tacit implication that a nosocomial infection occurs because something has been done wrong or neglected and better care would have prevented it.

In a series of patients in the surgical intensive-care unit (ICU) at the University of Iowa Hospitals, Pittet et al (1) assessed the duration of stay, extra costs, and attributable mortality that resulted from bloodstream infections. In this case-control study, 4,002 patients were admitted to the surgical ICU between July 1988 and June 1990. In this overall group, 107 episodes of nosocomial bloodstream infections developed in 97 patients. There were 2.7 infections per 100 admissions and 8.6 episodes per 1,000 patient-days. Researchers reviewed the medical records of 86 cases and matched control patients for sex, age, primary diagnosis, and total number of diagnoses; there was a 95% match rate. When examined for crude mortality rate, the control group showed a mortality rate of 15% in comparison with 50% observed in patients with bloodstream infection. Thus, the attributable mortality due to bloodstream infections was 35%, and the relative risk ratio for death was 3.31 (Fig. 1). The duration of hospital stay for

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patients experiencing bloodstream infection was significantly longer than that noted for patients without bloodstream infection—40 days versus 26 days, respectively ($P<0.01$). Likewise, the median ICU stay for patients experiencing bloodstream infection (15 days) was twice as long as that for patients without infection (7 days) ($P<0.01$). In a subset of 41 matched pairs of patients who survived infection, the duration of hospital stay was 30 days for the uninfected group and 54 days for patients with bloodstream infections. Thus, bloodstream infection resulted in an excess duration of hospital stay of 24 days. The extra cost due to nosocomial bloodstream infection was found to be approximately \$33,000 per patient or \$41,000 per survivor. Adjusted to 2003 dollars, this represents a cost of \$100,000 per episode of bloodstream infection. Similar findings have been described in the United Kingdom; thus, nosocomial infections seem to be a worldwide problem (2).

Nosocomial infections constitute a serious health threat. They occur frequently, are associated with a high mortality, and are expensive to treat. Prevention and treatment of nosocomial infections are priorities for the Centers for Disease Control and Prevention (CDC) (3). Of note, none of the 12 guidelines endorsed by the CDC mentions modulation of host defenses, including avoidance of hyperglycemia.

ROLE OF HYPERGLYCEMIA IN NOSOCOMIAL INFECTIONS

There are numerous mechanisms by which hyperglycemia could have a role in promoting hospital-acquired infections. Humoral immunity depends on antibody function. Antibodies neutralize the effect of bacteria by attaching directly to the microbes and preventing attachment to

host cells. In addition, antibody attachment induces complement activation and aids in the eventual phagocytosis of bacteria by host leukocytes. After ingestion, phagocytes become stimulated and create an oxidative burst that is lethal to microbes. The process of phagocytosis has been studied extensively in patients with diabetes.

In 1971, Mowat and Baum (4) measured the chemotactic index in 31 patients with diabetes and control subjects and found that chemotaxis was severely impaired in the patients with diabetes. Furthermore, the incubation of the impaired leukocytes with insulin in vitro (1 to 10 U/dL) corrected the defect. Nielson and Hindson (5), who studied the effect of hyperglycemia on the oxidative burst in vitro, found that when polymorphonuclear leukocytes were isolated from healthy volunteers and cultured in vitro with increasing concentrations of glucose, the polymorphonuclear leukocyte respiratory burst was reduced after a 30-minute incubation in a glucose concentration of 200 mg/dL. Although the consequences of the impaired respiratory burst described are unclear, disease states that reduce this leukocyte function have been associated with decreased antimicrobial activity in vitro and with an increased incidence of infection in vivo.

Similar findings were reported by Bagdade et al (6) in a study in 1974. When polymorphonuclear leukocytes from healthy subjects were cultured in increasing concentrations of glucose, progressive deterioration in both phagocytic and bactericidal activity was noted with increasing glucose concentrations. They also performed in vivo studies, which showed impaired phagocytic and antimicrobial function in patients with poorly controlled diabetes. Furthermore, they observed an improvement in immunologic function after treatment yielded enhanced glycemic control (Fig. 2). In 1974, treatment of diabetes

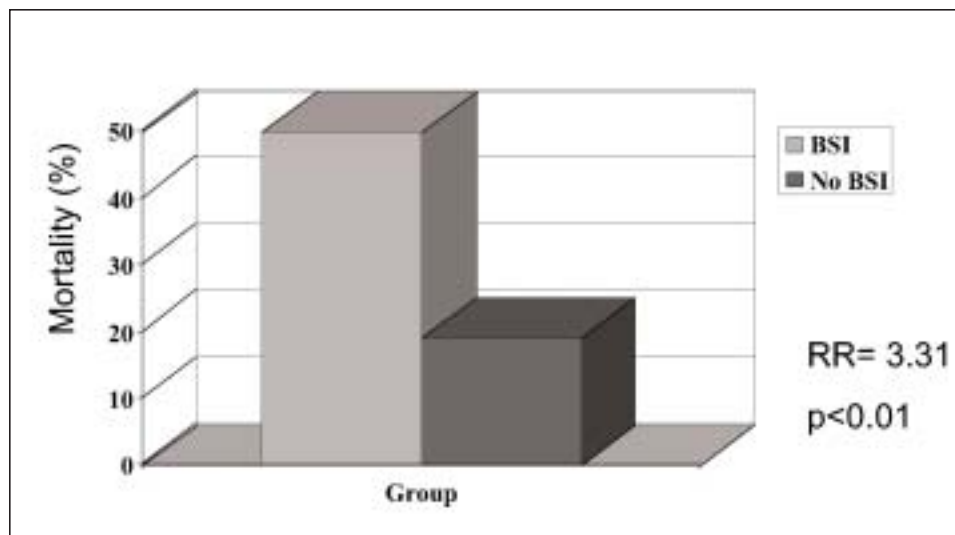


Fig. 1. Effect of bloodstream infection (BSI) on crude mortality among patients in the surgical intensive-care unit who had been admitted to the University of Iowa Hospitals between July 1, 1988, and June 30, 1990. Cases were defined as patients with nosocomial bloodstream infection; control patients (without bloodstream infection) were selected by matching variables in a stepwise fashion. Data from *JAMA* (1).

consisted of diet, sulfonylurea agents, and insulin—regular, NPH, or Lente. The details of treatment were not provided in this study, but intensive treatment with agents such as thiazolidinediones or the newer insulins may facilitate better glycemic control.

Although the focus thus far has been on the effect of hyperglycemia on polymorphonuclear leukocyte function, the deleterious effects of hyperglycemia are not that limited. Hennessey et al (7) demonstrated that nonenzymatic glycosylation of immunoglobulin impairs complement fixation. More recent studies, which used streptozotocin-induced diabetic rats, demonstrated that after 12 weeks of hyperglycemia, serum advanced glycation end products were almost double those seen in control animals (8). Native rat IgG, incubated in the presence of advanced glycation end product peptides from diabetic animals, displayed modification of light chains after only 24 hours of incubation (9). Thus, in addition to adverse effects on polymorphonuclear leukocyte function, hyperglycemia can impair immunoglobulin and complement function through nonenzymatic glycosylation.

Numerous clinical studies have reported that hyperglycemia is associated with increased rates of infectious complications. Rayfield et al (10) performed an outpatient observational review of medical records to determine whether a relationship existed between glycemic control and infections. In this study, 241 patients with diabetes underwent surveillance during a 1-year observation period in which at least three office visits revealed that no infection was present. All patients were treated with one of three regimens—diet, orally administered agents, or insulin. A plasma glucose level was determined at each visit. Inpatient and emergency department visits were reviewed. Infection was said to be present if more than two of the following factors were documented: (1)

positive Gram stain; (2) positive culture; (3) fever; (4) leukocytosis with a shift to the left; (5) abnormal x-ray findings; (6) clinical documentation, such as a description of an abscess or cellulitis; and (7) response to treatment. A significant correlation was found between poorer glucose control and an increasing rate of infections ($P < 0.001$). No correlation was evident between infection and age, duration of diabetes, or presence of microvascular or macrovascular complications.

More recent clinical observations support a strong, if not causal, relationship between hyperglycemia and infection. Trick et al (11) studied harvest site infection of the radial arteries in patients undergoing a coronary artery bypass grafting procedure. They found that, in patients with diabetes, a preoperative blood glucose level ≥ 200 mg/dL and the duration of the surgical procedure were independent risk factors for infection of the radial artery harvest site. Pomposelli et al (12) found that hyperglycemia on postoperative day 1 was associated with a threefold increase of all nosocomial infections in patients with diabetes undergoing an elective operation. Furnary et al (13) demonstrated reduction in the rate of deep sternal wound infection after cardiac surgical procedures in patients with better glycemic control.

Hyperglycemia, defined as a fasting blood glucose level of more than 126 mg/dL or a random blood glucose value in excess of 140 mg/dL, is extremely common among hospitalized patients. At Hartford Hospital (Hartford, Connecticut), a large tertiary care facility, diabetes is a comorbid condition in 30 to 35% of admissions (and somewhat higher if healthy obstetric patients are excluded). In addition, many patients without diabetes have transient hyperglycemia in response to metabolic stress or treatments with certain drugs such as glucocorticoids. For example, of our 1,000 patients undergoing

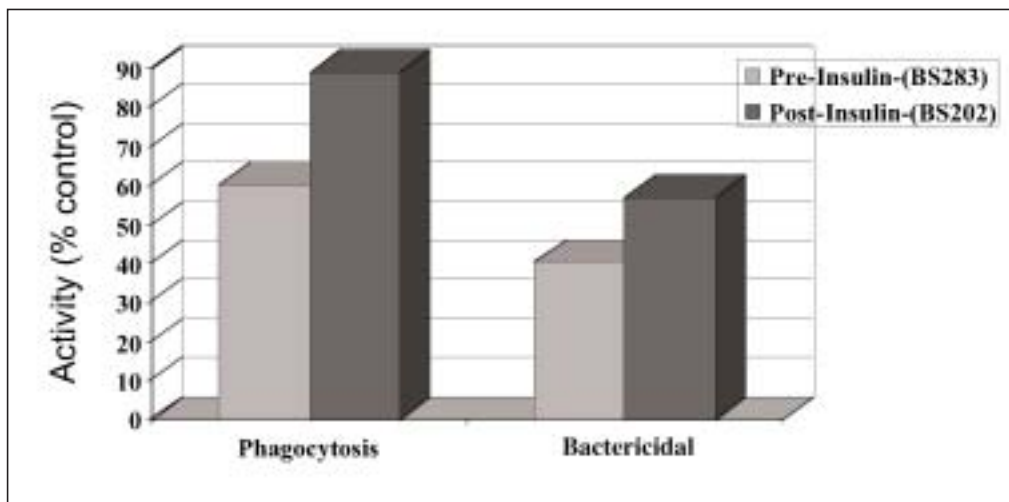


Fig. 2. Effect of hyperglycemia on leukocyte function in vivo. Polymorphonuclear leukocytes were isolated from venous blood from eight patients with poorly controlled, nonketotic diabetes before and after treatment with regular insulin. Phagocytic and bactericidal activities were tested by using type 25 pneumococcal organisms. Data from *Diabetes* (6).

cardiac surgical procedures annually, approximately a third have transient hyperglycemia for which they receive insulin therapy.

In summary, these data show a relationship between infection and hyperglycemia, but no studies have addressed the issue of cause and effect. Does hyperglycemia occur because of infection, or does hyperglycemia lead to infection? None of the aforementioned studies was randomized and controlled. Therefore, we will present some findings from a prospective, randomized, controlled clinical trial that was performed in the surgical ICU to address the cause-and-effect relationship between hyperglycemia and nosocomial infections in the surgical ICU.

Patients in the surgical ICU environment experience severe physiologic stress and are known to have an increased risk of nosocomial infection and death. Well-described alterations in pathways of intermediary metabolism are common in these patients with physiologic stress and are independent of the cause of the underlying disease. Hyperglycemia is a biochemical hallmark of this altered physiologic state. Until recently, mild to moderate increases in blood glucose levels to 150 to 250 mg/dL were common and generally thought to be of little consequence in the everyday management of the critically ill surgical patient.

Our hypothesis was that strict glycemic control will decrease the rate of nosocomial infections in patients in the surgical ICU. The primary objective of our study was to compare the incidence of nosocomial infection between two matched groups of patients—those administered an intravenous insulin infusion to achieve standard glycemic control with a target blood glucose range of 180 to 220 mg/dL and those maintained with strict glycemic control in the blood glucose range of 80 to 120 mg/dL. Of note, at the time this study was performed, many clinicians would have considered a glucose level in the range of 180 to 220 mg/dL as good glycemic control.

METHODS

Study Design

A prospective, randomized, controlled clinical trial was conducted with the approval of the institutional review board at Hartford Hospital. Written informed consent was obtained from eligible adult patients admitted to a 12-bed general surgical ICU who required treatment for hyperglycemia. Randomization to receive standard glucose control or strict glucose control was determined by coin toss. Patients expected to have a brief stay or not expected to survive beyond 48 hours were excluded from the study, as were those with active infections, with disseminated cancer, or receiving chemotherapy, irradiation, or corticosteroids. All patients received care and intervention considered standard practice, as directed by the patient's physician in consultation with a board-certified

surgical intensivist. All infections were treated by culture-directed antimicrobial therapy.

Glycemic Control

Intravenous insulin infusions were administered to maintain serum glucose values in the range of 180 to 220 mg/dL in the standard control group and from 80 to 120 mg/dL in the strict control group. Insulin infusions were managed by surgical ICU nurses and adjusted according to an algorithm designed for this study. Investigators made rounds to see these patients twice daily and were available for telephone consultation 24 hours a day. The frequency of blood glucose measurement was based on insulin algorithms and supplemented by clinical judgment, as determined by the nurse at the bedside. Nutritional support was managed for all patients by a critical care nutritional support team, with use of standard guidelines.

Outcomes

Outcome measures included serum glucose values and incidence of nosocomial infection. Nosocomial infections were defined in accordance with the CDC classification (14). Nosocomial infection rates were recorded as intravascular device infection (IVDI), bloodstream infection, surgical site infection, pneumonia, or urinary tract infection per 1,000 surgical ICU days. Device days were not specifically determined, but all patients had an indwelling urinary catheter and at least one central venous catheter in place throughout the duration of the surgical ICU stay.

RESULTS

The study was completed by 61 critically ill patients, including 27 in the standard glucose control group and 34 in the strict glucose control group. The clinical characteristics of patients were similar between the two study groups with respect to age, sex, body mass index, ethnicity, incidence of diabetes, presence of comorbidities, duration of surgical ICU stay, proportion receiving parenteral nutrition, APACHE (acute physiologic assessment and chronic health evaluation) score, American Society of Anesthesiologists score, blood transfusion history, initial serum glucose value, and antimicrobial administration (Table 1). Data for the group of patients with standard control of serum glucose included 2,200 glucose determinations and 728 microbial cultures during 663 ICU days. Data for the patients with strict control of serum glucose included 3,500 glucose determinations and 302 microbial cultures during 761 ICU days.

Glycemic Control

Mean serum glucose values at the time of study enrollment were not significantly different between the two study groups; 165 ± 67 mg/dL for the standard glucose control group versus 153 ± 46 mg/dL for the strict

Table 1
Demographic Data for 61 Study Patients,
Stratified by Standard or Strict Control of Serum Glucose*†

Variable	Standard glucose control	Strict glucose control	P
No. of patients	27	34	...
Mean age (yr)	55 ± 22	56 ± 22	0.93
Female:male (%)	37:63	25:75	0.27
BMI (kg/m ²)	27.5 ± 6.1	27.9 ± 6.3	0.83
ASA score ≥III (%)*‡	91	100	0.13
APACHE II score§	15.6 ± 7.4	15.1 ± 6.5	0.79
Diabetes (%)	11	13	0.73
Corticosteroids (%)	30	21	0.42
Vasopressor (%)¶	44	54	0.46
Renal replacement (%)¶¶	10	3	0.31
Hospital mortality (%)	21	11	0.50
Mean SICU stay (days)	24.5 ± 19.4	33.4 ± 68.3	0.52

*APACHE = acute physiologic assessment and chronic health evaluation; ASA = American Society of Anesthesiologists; BMI = body mass index; SICU = surgical intensive-care unit.

†Standard control = serum glucose values maintained at 180-220 mg/dL; strict control = serum glucose values maintained at 80-120 mg/dL.

‡Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. *Anesthesiology*. 1978;49:239-243.

§Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE—acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med*. 1981;9:591-597.

¶Vasopressors = α -adrenergic agonists, including dopamine >2 mg/kg/min.

¶¶Provided by continuous venovenous hemofiltration.

glucose control group. The group mean for all glucose levels was significantly less in the strict glucose control group (125 ± 36 mg/dL) than in the standard glucose control group (179 ± 61 mg/dL) ($P < 0.001$) (Fig. 3). The daily mean glucose values for the 31 ICU days were determined for each study group. The mean glucose value in the strict glucose control group was significantly lower than in the standard glucose control group for all days. Most serum glucose values for the standard glucose control group showed hyperglycemia, whereas 72% of serum glucose values for the strict glucose control group were in the range of 60 to 149 mg/dL. Episodes of hypoglycemia (glucose values <60 mg/dL) occurred in 32% of the patients (0.8% of the total serum glucose values) in the strict glucose control group in comparison with 7.4% of the patients (0.1% of serum glucose values) in the standard glucose control group ($P < 0.001$). Episodes of hypoglycemia were not associated with major clinical complications.

Nosocomial Infections

The number of diagnostic and microbial studies did not differ between the two study groups. Bloodstream infections, IVDI or IVDI-related bloodstream infections,

and surgical site infections developed in a significantly higher percentage of patients in the standard glucose control group than in the strict glucose control group (Fig. 4). These data were adjusted for the variable durations of stay of individual patients and presented as an infection rate per 1,000 patient-ICU days. A 4-fold increase in IVDI and bloodstream infections was noted in the standard glucose control group ($P < 0.05$); also observed was a 3.5-fold increase in IVDI-related bloodstream infections and surgical site infections ($P < 0.05$). Although not statistically significant, a trend toward increased rates of urinary tract infection and nosocomial pneumonia was evident in the standard glucose control group.

DISCUSSION

These results show that hyperglycemia (that is, serum glucose levels of >180 mg/dL) can predispose critically ill surgical patients to the development of nosocomial infections. Furthermore, intravenous treatment with insulin to reduce the serum glucose concentration can lead to a significant reduction in the rates of nosocomial infections in patients in the surgical ICU. In light of the fact that 90% of our patients did not have diabetes, hyperglycemia per se

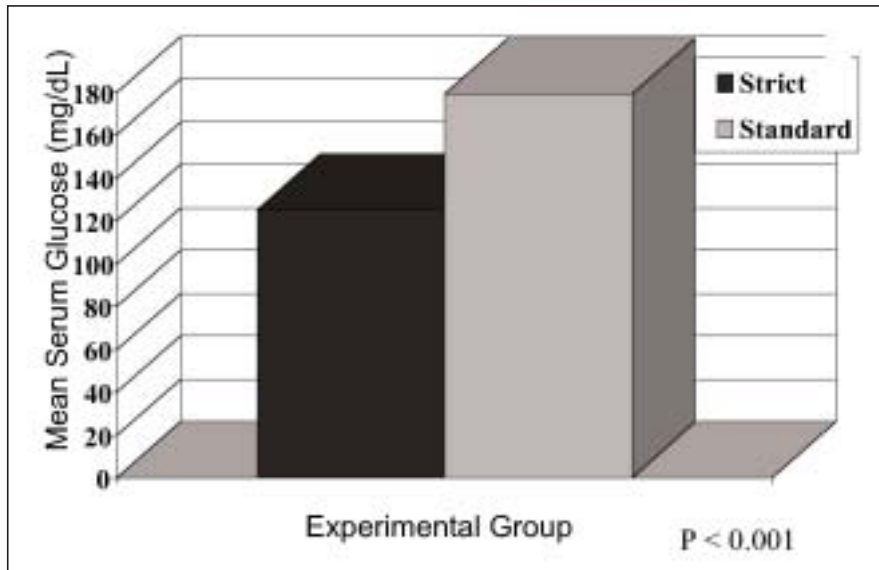


Fig. 3. The group mean for all serum glucose values was significantly less ($P < 0.001$) in the strict glucose control group (125 ± 36 mg/dL [range, 41 to 400], $N = 3,503$) in comparison with the standard glucose control group (179 ± 61 mg/dL [range, 38 to 468], $N = 2,195$). The mean serum glucose level per patient and the daily mean, daily maximum, and daily minimum serum glucose values for each group were also significantly less for those with strict glycemic control than for those with standard control ($P < 0.001$) (data not shown).

is a potentially serious problem for all patients (not just those with diabetes) who require surgical intensive unit care. This study does not address mechanisms by which hyperglycemia leads to increased nosocomial infections, nor does it distinguish between a direct and an indirect effect of insulin on these outcomes.

CONCLUSION

This report demonstrates that the historical observations that linked hyperglycemia to immunologic dysfunction do, indeed, translate into greater risk for development of nosocomial infections. Avoidance of hyperglycemia by

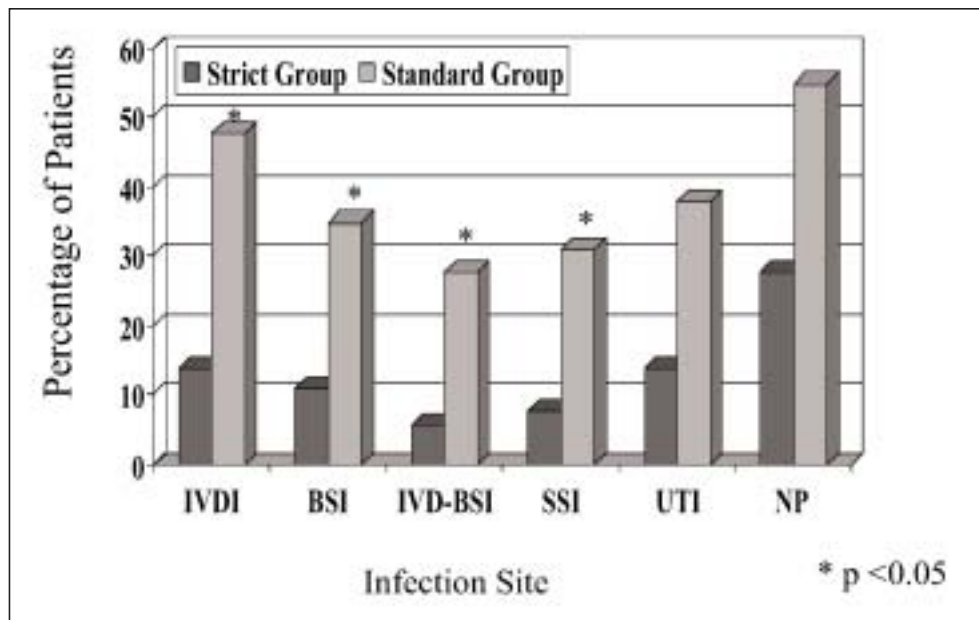


Fig. 4. Reduction in various nosocomial infections by strict glycemic control. Results are shown for intravascular device infections (IVDI), bloodstream infections (BSI), intravascular device-related bloodstream infections (IVD-BSI), surgical site infections (SSI), urinary tract infections (UTI), and nosocomial pneumonia (NP). Nosocomial infections were defined in accordance with the Centers for Disease Control and Prevention classification (14).

intravenous insulin therapy reduced nosocomial infections in the high-risk surgical ICU patient population.

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