Relationship Between Hyperglycemia and Infection in Critically Ill Patients

Simona O. Butler, Pharm.D., Imad F. Btaiche, Pharm.D., and Cesar Alaniz, Pharm.D.

Hyperglycemia is a common problem encountered in hospitalized patients, especially in critically ill patients and those with diabetes mellitus. Uncontrolled hyperglycemia may be associated with complications such as fluid and electrolyte disturbances and increased infection risk. Studies have demonstrated impairment of host defenses, including decreased polymorphonuclear leukocyte mobilization, chemotaxis, and phagocytic activity related to hyperglycemia. Until 2001, hyperglycemia (blood glucose concentrations up to 220 mg/dl) had been tolerated in critically ill patients not only because high blood glucose concentrations were believed to be a normal physiologic reaction in stressed patients and excess glucose is necessary to support the energy needs of glucose-dependent organs, but also because the true significance of short-term hyperglycemia was not known. Recent clinical data show that the use of intensive insulin therapy to maintain tight blood glucose concentrations between 80 and 110 mg/dl decreases morbidity and mortality in critically ill surgical patients. Intensive insulin therapy minimizes derangements in normal host defense mechanisms and modulates release of inflammatory mediators. The principal benefit of intensive insulin therapy is a decrease in infection-related complications and mortality. Further research will define which patient populations will benefit most from intensive insulin therapy and firmly establish the blood glucose concentration at which benefits will be realized.

Key Words: hyperglycemia, infection, diabetes mellitus, critical illness, glucose metabolism, intensive insulin therapy.

(Pharmacotherapy 2005;25(7):963–976)

OUTLINE

From the Department of Pharmacy Services, University of Michigan Hospitals and Health Centers (all authors), and the Department of Clinical Sciences, University of Michigan College of Pharmacy (Drs. Btaiche and Alaniz), Ann Arbor, Michigan.

Address reprint requests to Simona O. Butler, Pharm.D., Department of Pharmacy Services, University of Michigan Hospitals and Health Centers, UH B2D301, Box 0008, 1500 East Medical Center Drive, Ann Arbor, MI 48109.

Hyperglycemia is a common problem encountered in hospitalized patients, especially in critically ill patients and those with diabetes mellitus. Risk of hyperglycemia is increased in patients receiving concentrated dextrose infusions such as parenteral nutrition. Uncontrolled

hyperglycemia may be associated with complications such as fluid and electrolyte disturbances and increased infection risk. Controlling hyperglycemia reduces microvascular and macrovascular complications in patients with diabetes[1–6] and reduces nosocomial and wound infections in perioperative hyperglycemic and diabetic patients.[7–16] However, a cause and effect relationship between sepsis and hyperglycemia has long been debated. Although it has been clearly documented that sepsis induces hyperglycemia, the effects of hyperglycemia on increasing infection risk had not been fully elucidated.[17] Until 2001, blood glucose concentrations up to 220 mg/dl had been tolerated in critically ill patients.[18, 19] This was essentially based on the belief that high blood glucose concentrations were a normal physiologic reaction in stressed patients, and excess glucose was necessary to support the energy needs of glucose-dependent organs such as the brain, adrenal medulla, and red blood cells. However, recent data show that the use of intensive insulin therapy to maintain tight blood glucose concentrations between 80 and 110 mg/dl decreases morbidity and mortality in critically ill surgical patients. The benefits of tight glucose control also extend to significant reductions in several morbidity factors including infection rate.[20]

Normal Glucose Metabolism

Glucose metabolism involves complex metabolic reactions to maintain glucose homeostasis. Exogenous glucose sources include dietary carbohydrates or dextrose infusions. Endogenous glucose sources include glycogen stores that release glucose through liver glycogenolysis and from noncarbohydrate precursors (e.g., lactate, alanine, glycerol) that are converted to glucose through gluconeogenesis mainly in the liver and to a lesser extent in the kidneys. The brain, red blood cells, and renal medulla depend on glucose for energy by non–insulin-mediated uptake mechanisms.[21] Under basal conditions, these glucose-dependent tissues consume about 50–80% of ingested glucose.[22, 23] The remaining glucose is converted to produce energy through glycolysis, stored as glycogen in the liver and skeletal muscles, or converted to fat in the liver and adipose tissues.[22, 23]

Blood glucose concentrations are controlled by hormonal, neural, and hepatic autoregulatory mechanisms. In a healthy individual, blood glucose concentrations are tightly regulated within a narrow range of about 80–100 mg/dl. Hormonal mechanisms are exerted by insulin and the counterregulatory hormones, which include glucagon, catecholamines, cortisol, and growth hormone. Effects of insulin are exerted mainly through its anabolic function to increase glucose uptake and storage.[21, 24] Insulin effects are also mediated through its antiinflammatory suppression of proinflammatory cytokine (e.g., tumor necrosis factor-α, interleukin [IL]-1, and IL-6) production and signaling[25–28] to lower blood glucose concentrations by stimulating glucose uptake and glycogen synthesis, and inhibiting glyconeogenesis.[21, 22, 24, 29]

Counteracting the anabolic effects of insulin are the counterregulatory hormones that stimulate glycogenolysis and gluconeogenesis and inhibit insulin-mediated glucose uptake.[21–23] Neural mechanisms involve central and peripheral glucosensors that monitor glucose availability and respond to changes in blood glucose concentration by releasing insulin or inhibiting insulin secretion. Hepatic autoregulation responds directly to increased blood glucose concentration by decreasing its glucose production.[22]

Glucose Metabolism in Critical Illness

Significant alterations to glucose metabolism occur under conditions of stress such as trauma, burn, major surgery, and sepsis. Stress-induced hyperglycemia is the result of increased sympathomimetic activity and increased release of counterregulatory hormones and proinflammatory cytokines. Counterregulatory hormones enhance glycogenolysis and gluconeogenesis to increase glucose production. For instance, epinephrine enhances glycogenolysis in the liver and skeletal muscles and increases gluconeogenesis in the kidneys. Growth hormone inhibits peripheral glucose uptake and stimulates gluconeogenesis. Proinflammatory cytokines are inflammatory mediators that also contribute to increasing glucose production by stimulating gluconeogenesis and glycogenolysis and by indirectly increasing the release of counterregulatory hormones such as glucagon and cortisol. Furthermore, proinflammatory cytokines contribute to insulin resistance by inhibiting insulin release. The end result of these physiologic changes is increased endogenous glucose production coupled with insulin resistance that leads to stress-induced hyperglycemia.[21–23, 30, 31]

Patients receiving dextrose infusions, especially those administered as part of parenteral nutrition,

are at highest risk for developing hyperglycemia. However, other risk factors also predispose patients to hyperglycemia; these include underlying conditions such as diabetes mellitus, acute pancreatitis, and obesity, as well as drugs such as catecholamine vasopressors (e.g., dopamine, norepinephrine), immunosuppressants (e.g., tacrolimus, cyclosporine), and corticosteroids[17] (Figure 1).

Hyperglycemia

Definition

The definition of diabetic hyperglycemia was most recently revised in 1997 by the Expert Committee on Diagnosis and Classification of Diabetes Mellitus: diabetic hyperglycemia is diagnosed based on symptoms of diabetes and a random plasma blood glucose concentration higher than 200 mg/dl, a fasting blood glucose concentration of 126 mg/dl or higher, or a 2-hour post-load blood glucose concentration higher than 200 mg/dl.[32] As previously stated, however, hyperglycemia in the critically ill patient is less clearly defined, and the notion of the beneficial effects of hyperglycemia is being challenged now in view of better patient outcomes with tighter glucose control to maintain euglycemia.[20]

Complications

In patients with diabetes, uncontrolled blood glucose concentration is associated with increased occurrence of microvascular complications (e.g., retinopathy, nephropathy, peripheral neuropathy) and macrovascular complications (e.g., atherosclerotic cardiovascular, peripheral vascular, and cerebrovascular diseases).[1–6, 19, 32] Hyperglycemia also leads to multiple adverse consequences including osmotic diuresis, fluid and electrolyte imbalances, hyperosmolar nonketotic coma, worsening skeletal muscle catabolism, impaired wound healing, changes in coagulability, impaired immune function, increased susceptibility to infections,[22, 30, 33] and death in certain surgical patients.[34]

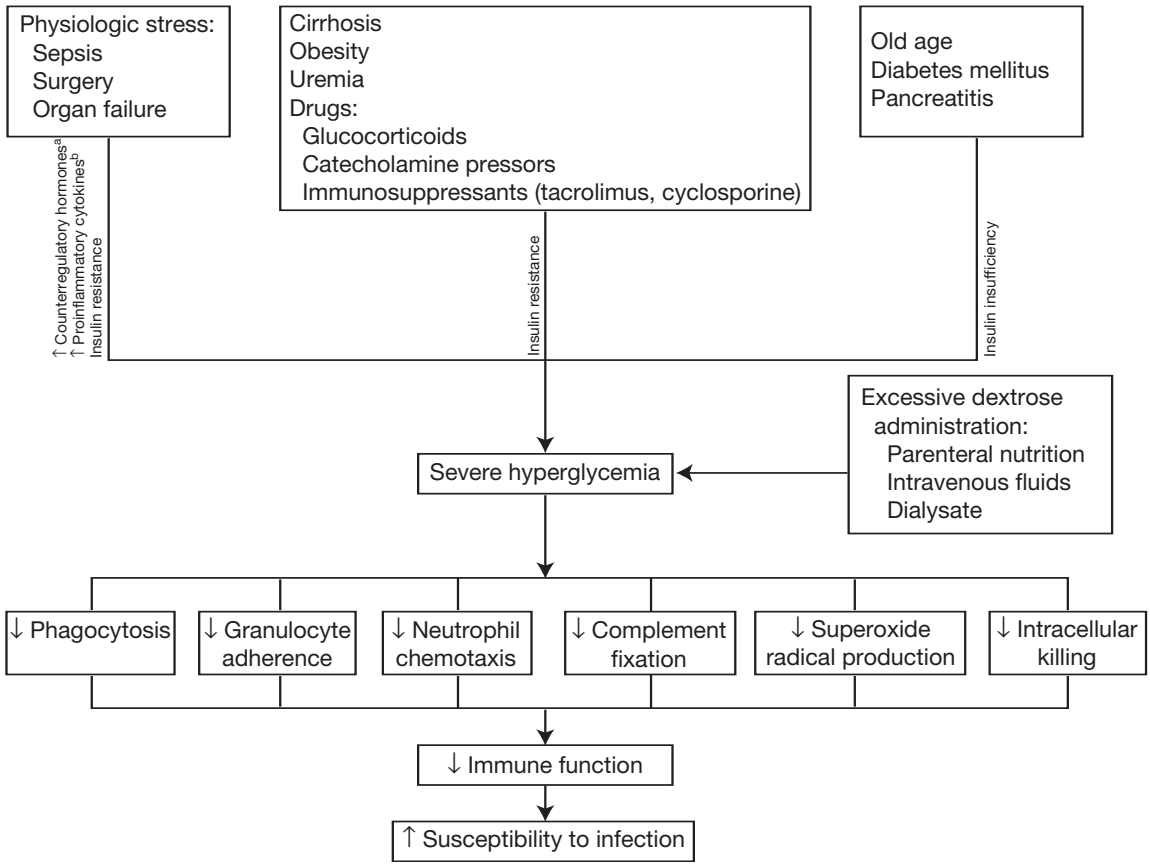

Figure 1. Causes of hyperglycemia and effects of hyperglycemia on increased susceptibility to infection in the critically ill patient. [a]Counterregulatory hormones are glucagon, catecholamines, cortisol, and growth hormone; [b]proinflammatory cytokines are tumor necrosis factor-α, interleukin (IL)-1, and IL-6.

Pathogenesis of Hyperglycemia-Associated Infection

A rise in the risk of postoperative infectious complications results from depressed immune function secondary to inhibition of IL-1 release from macrophages, impaired phagocytosis, and diminished production of oxygen radicals from neutrophils.[21, 35] As a result, studies addressed the effect of transient acute hyperglycemia in a nondiabetic rat model on immune function after surgery[36] or splenectomy.[37] The authors of the first study evaluated the function of peripheral neutrophils, peritoneal macrophages, and alveolar macrophages in postoperative nondiabetic rats in two groups: normoglycemic (control) and hyperglycemic.[36] Their results showed significant change in immune function based on blood glucose concentration.

The second study focused on demonstrating decreased immunologic activity in rats after splenectomy and induction of bacteremia in the setting of hyperglycemia.[37] Survival times were markedly lower in the hyperglycemic group. Consequently, the authors concluded that short-term exposure to high glucose concentration has detrimental effects to the immune function of the studied cells and could be one of the primary factors contributing to increased susceptibility to infection in this population. Furthermore, the effect of blood glucose control with exogenous insulin was determined in vivo in a study of rabbits with severe injury.[27] Results revealed improvement in phagocytosis and oxidative killing with prevention of weight loss, hyponatremia, lactic acidosis, and excessive inflammation in the group maintained at normoglycemia (60–110 mg/dl). Similar findings came from an in vitro study that showed significant reduction in polymorphonuclear leukocyte phagocytic activity of normal cells in intermittent hyperglycemia compared with control.[38]

Hyperglycemia and Infection in Patients with Diabetes

Blood glucose control was originally investigated in the setting of diabetes because diabetic patients seemed to be predisposed to various infections (e.g., cystitis, cellulitis, postoperative wound infections[10]) and infectious complications as a result of having diabetes.[39] Although the exact pathogenesis was unknown, it was speculated that the increased risk of infection was related to decreased cellular immune function.[10] Later studies (both in animals and humans) demonstrated that the depressed ability to fight off infection was a result of impaired polymorphonuclear leukocyte function, chemotaxis, and phagocytosis.[31, 39–43]

Studies in diabetic animals examined the phagocytic activity[44] and membrane fluidity[45] of certain immune cell types. Results showed impaired intracellular killing[44] and higher susceptibility to infection although decreased fluidity[45] in animals with poorly controlled diabetes compared with well-controlled ones. In vitro studies in diabetic patients further strengthened the evidence of cellular immune function impairment by demonstrating a significant reduction in polymorphonuclear leukocyte mobilization, chemotaxis, and bactericidal and phagocytic activity in poorly controlled[42, 46] diabetic cells compared with well-controlled ones[42, 46] and diabetic[47] cells in general compared with control.[47] Data derived from animal and in vitro trials led to further investigation of the link between hyperglycemia and infectious complications in patients with diabetes.

In 1991, one group of authors performed a retrospective chart review to compare operative mortality and complications (e.g., wound infections, myocardial infarction, arrhythmias, respiratory failure) in diabetic versus nondiabetic patients after coronary artery bypass graft (CABG).[7] Their analysis included 711 patients, 79% nondiabetic and 21% diabetic. The results did not show a difference between the two groups with respect to mortality but demonstrated a significantly increased morbidity in the diabetic group especially in the wound infection parameter.

Another group looked specifically at the rate of deep sternal wound infections in diabetic patients after cardiac surgery in a before and after retrospective chart review.[8] A strict blood glucose control protocol was implemented, with a target of blood glucose concentration less than 200 mg/dl. A total of 999 patients had surgery before the protocol was implemented, and 595 had surgery after. The results revealed a significant reduction in deep wound infection after protocol implementation, with elevated blood glucose level being directly related to infection rate. Later, these authors further demonstrated that the use of perioperative continuous intravenous infusion in this patient population significantly reduced morbidity from deep sternal wound infections and the costs associated with it.[11]

An increased rate of nosocomial infection in

diabetic patients undergoing elective surgery was demonstrated in 1998. This was a noninterventional study with the objective to determine the relationship between perioperative glucose control (good blood glucose level was defined as < 220 mg/dl) and postoperative infection rate.[9] Analysis of 93 patients and their serum glucose concentrations on postoperative day 1 indicated that the nosocomial infection rate was 2.7 times higher in diabetic patients with a blood glucose level above 220 mg/dl and 5.7 times higher when urinary tract infections were eliminated compared with patients with better glucose control. Thus, these authors concluded that a blood glucose level above 220 mg/dl was a sensitive predictor (87.5%) of nosocomial infection.

Finally, in 1999, another group performed a nonconcurrent, prospective, cohort, blinded study with the purpose of assessing the independent relationship between perioperative glycemic control and subsequent risk of infectious complications (e.g., pneumonia, urinary tract infection, wound infection) on postoperative day 2 or later in diabetic patients undergoing coronary artery surgery.[10] Their results echoed those of the previous studies and showed an increased infection rate in patients with a perioperative blood glucose level higher than 200 mg/dl. There was no relationship between peak perioperative blood glucose level and subsequent risk of infectious complications. Table 1 summarizes the studies relating hyperglycemia with infection and mortality in the surgical and critically ill patient population.

Hyperglycemia and Infection in Critically Ill Patients

As evidence accumulated in support of tight glycemic control in patients with diabetes, there still remained significant controversy regarding the pathophysiology and management of stress-induced hyperglycemia. Increased glucose turnover and insulin resistance were regarded as potentially appropriate responses during critical illness.[22] Also, although the association between hyperglycemia and infection had been well established,[31] debate continued regarding which condition precipitated the other.[51] However, data are now emerging that provide important information on the consequences and management of hyperglycemia in critically ill patients.[20]

In 2001, a group of authors published the results of a large, prospective, randomized, controlled trial that was the first to challenge the accepted clinical practice of loose glycemic control in critically ill patients.[20] During a 1-year period, 1548 patients with mechanical ventilation who were admitted to an intensive care unit (ICU) after surgery or trauma were randomly assigned to either intensive insulin or conventional therapy. The conventional therapy group was targeted to maintain a blood glucose level of 180–200 mg/dl with insulin therapy to begin at a blood glucose level higher than 215 mg/dl, with the insulin dose adjusted by the nursing staff. The intensive insulin therapy group was targeted to maintain a blood glucose level at 80–110 mg/dl with insulin therapy to begin at a blood glucose level higher than 110 mg/dl following a strict algorithm.

Hypoglycemia was defined as a blood glucose level less than 40 mg/dl. After discharge from the ICU, both groups were switched to subcutaneous insulin with a target blood glucose level of less than 200 mg/dl. The primary outcome was all-cause ICU mortality and secondary outcomes included in-hospital mortality, number of ICU and ventilation days, ICU stay longer than 14 days or readmission, use of renal replacement therapy and inotropic or vasopressor support, occurrence of infections, and critical illness polyneuropathy.

Results showed that use of intensive insulin therapy was associated with a 34% decrease in overall in-hospital mortality. The ICU mortality rate decreased from 8% to 4.6% (> 40% reduction), with the effect occurring primarily in patients in the ICU for more than 5 days (intensive therapy group 10.6% mortality vs 20.2% mortality in conventional therapy group). After adjustment for repeated interim analyses, the median unbiased estimate of mortality reduction was 32% (adjusted 95% confidence interval 2–55%, $p<0.04$). No significant difference was noted in mortality between the two groups within the first 5 days in ICU. Furthermore, tight blood glucose control significantly decreased morbidity as demonstrated by a reduction in the duration of ventilatory support and ICU stay, reduced need for blood transfusions, 46% reduction in frequency of sepsis, decreased frequency of excessive inflammation, 44% reduction in polyneuropathy, and 41% reduction in acute renal failure. The overall conclusion was that use of exogenous insulin to maintain a blood glucose level below 110 mg/dl reduced morbidity and ICU and in-hospital mortality among surgical

Table 1. Infection Rate and Mortality in Clinical Trials of Hyperglycemia and Infection in Surgical and Critically Ill Patients

Trial Design (year)	Study Type	Patient Population	Primary End Point	Results
Nonrandomized, retrospective (1991)[7]	Observational	Diabetic and nondiabetic patients undergoing CABG (n=711, 146 diabetic vs 565 nondiabetic patients)	Mortality within 30 days of surgery or during same hospitalization	No difference in mortality. Higher morbidity and wound infection rate in diabetic vs nondiabetic patients.
Prospective, nonrandomized, cohort (1998)[9]	Observational	Diabetic patients undergoing elective surgery (n=93)	Relationship between glucose control and development of postoperative nosocomial infections (bacteremia, UTI, pneumonia, surgical wound infection, intraabdominal abscess, *Clostridium difficile* colitis)	Higher infection rate (except for UTI) in patients with BGL > 220 mg/dl vs BGL < 220 mg/dl on post-operative day 1.
Nonconcurrent, prospective, cohort, blinded (1999)[10]	Observational	Diabetic patients undergoing CABG (n=411)	Relationship between peri-operative glycemic control and development of post-operative infectious complications (pneumonia, UTI, wound infection, other) on day 2 or ≥ 36 hrs after surgery	Higher overall infection rate and infectious complications corresponding to higher BGL.
Nonrandomized, retrospective, case-control (2000)[12]	Observational	Diabetic and nondiabetic patients undergoing CABG (n=120, 30 case patients with deep sternal site infection, 90 control patients)	Deep sternal site infection rate before and during study period	Lower deep sternal site infection rate before vs during study period.
Nonrandomized, retrospective, case-control (2000)[13]	Observational	Diabetic and nondiabetic patients undergoing radial artery graft for revascularization during CABG (n=127, 35 case patients, 92 control patients)	Development of radial artery harvest site infection after CABG during heightened and routine postdischarge surveillance	Higher rate of radial artery harvest site infection during heightened vs routine surveillance.
Prospective, cohort, blinded, case-control (2001)[14]	Observational	Patients with known DM, unknown DM, and non-diabetic patients with hyperglycemia undergoing CABG or cardiac valve procedure (n=1044, 300 with known DM, 700 with unknown DM, 44 DM status not mentioned; 74 infected, 970 control)	Development of surgical site infection as related to BGL control (BGL and hemoglobin A_{1c})	Frequency of surgical site infections directly and significantly correlated with degree of hyperglycemia during postoperative period. Higher surgical site infection rate in patients with known DM vs patients with unknown DM. Higher surgical site infection rate in patients with known and unknown DM and nondiabetic patients.
Retrospective, cohort (2002)[15]	Observational	Diabetic and nondiabetic patients undergoing CABG (n=1090, 400 diabetic, 690 nondiabetic patients)	Postoperative infectious complications (deep and superficial sternal wound infection, donor site infection, UTI, lung infection) as related to peri- and postoperative glycemic control	Diabetic: higher perioperative BGL correlated with higher deep sternal wound infection rate. Higher postoperative infection rate (deep sternal wound infection, donor site infection, UTI) in diabetic vs nondiabetic patients. Higher early mortality in diabetic vs nondiabetic patients.

Table 1. Infection Rate and Mortality in Clinical Trials of Hyperglycemia and Infection in Surgical and Critically Ill Patients (continued)

Trial Design (year)	Study Type	Patient Population	Primary End Point	Results
Historic cohort (2003)[16]	Observational	Diabetic and nondiabetic patients undergoing CABG (n=1574, 545 diabetic, 1029 nondiabetic patients)	30-day mortality, 30-day infections (harvest site, sepsis, pneumonia, UTI, deep sternal wound infection), resource utilization as related to perioperative hyperglycemia	Higher overall infection rate in diabetic vs nondiabetics patients. Higher mortality in patients who developed infection in both groups.
Prospective, one center (2003)[48]	Observational	Diabetic and nondiabetic patients admitted to cardiothoracic, cardio-respiratory surgery and medicine ICU (n=523)	ICU mortality	In all glucose bands, increased insulin administration corresponded with significantly increased risk of ICU death.
Retrospective, longitudinal, one center (2003)[49]	Observational	Diabetic and nondiabetic patients admitted to general medical, surgical, and coronary ICU (n=1826)	Hospital mortality	Higher BGL corresponded with higher hospital mortality.
Nonrandomized, retrospective (1997)[8]	Interventional; insulin protocol: BGL goal < 200 mg/dl	Diabetic and nondiabetic patients undergoing cardiac surgery (n=8910, 1585 diabetic, 7325 nondiabetic patients)	Deep sternal wound infection rate before and after diabetic protocol	Diabetic: higher deep sternal wound infection rate before vs after protocol. Nondiabetic: higher deep sternal wound infection rate before vs after protocol.
Nonrandomized, prospective (1999)[11]	Interventional; insulin protocol: BGL goal 150–200 mg/dl	Diabetic patients undergoing open-heart surgery (n=2467, 968 control, 1499 continuous insulin infusion)	Infection (deep and superficial sternal wound infection, donor site infection) rate as related to postoperative BGL before and after protocol	Higher deep sternal wound infection rate in control vs continuous insulin infusion group.
Prospective, randomized, controlled (2001)[20]	Interventional; insulin protocol: intensive group BGL goal 80–110 mg/dl; conventional group: BGL goal 180–200 mg/dl	Diabetic and nondiabetic surgical ICU patients (n=1548, 765 intensive insulin, 783 conventional insulin)	Death from any cause during ICU stay	Lower overall ICU mortality, lower mortality in patients in ICU > 5 days, lower overall in-hospital mortality, lower in-hospital mortality in patients in ICU > 5 days, lower frequency of septicemia, prolonged antibiotics, and bacteremia in intensive vs conventional group.
Nonrandomized, historic control (2004)[50]	Interventional; insulin protocol: BGL goal ≤ 140 mg/dl	Diabetic and nondiabetic surgical and medical ICU patients (n=1600, 800 historic control, 800 treatment group)	In-hospital mortality before and after protocol	Lower hospital mortality after protocol implementation. Infection rate similar before and after protocol.

CABG = coronary arterial bypass graft; BGL = blood glucose level; UTI = urinary tract infection; DM = diabetes mellitus; ICU = intensive care unit.

critically ill patients regardless of their history of diabetes.

This study demonstrated that tight glycemic control can prevent infections and associated complications in critically ill surgical patients. Sixty-one patients (7.8%) developed sepsis

(bacteremia with systemic inflammatory response syndrome) in the conventional therapy group compared with 32 patients (4.2%) in the intensive insulin therapy group (p<0.003). In addition to the decrease in the frequency of septicemia, mortality from multiorgan failure with a proven septic focus decreased from 4.2% to 1.0%. Indeed, this subgroup represented the patient population that had the greatest reduction in death with intensive insulin therapy. Further, patients in the intensive insulin therapy group were less likely to receive prolonged antibiotics. One hundred thirty-four patients (17.1%) received antibiotics for more than 10 days in the conventional therapy group compared with 86 patients (11.2%) in the intensive insulin therapy group (p<0.001).

In 2003, the same group of authors addressed the issue of the relative impact of insulin dosage versus blood glucose concentration and their contributions to the demonstrated outcome benefits.[25, 26] Results showed that control of hyperglycemia, rather than dosage of insulin, was associated with the beneficial outcomes of decreases in mortality, bacteremia, polyneuropathy, inflammation, and anemia, but not to the prevention of acute renal failure. The data also showed that there was no specific threshold below which no further risk reduction occurred. When patients were stratified according to glucose concentration, even moderate hyperglycemia (110–150 mg/dl) was associated with significantly increased risk of bacteremia and mortality. The authors speculated that the association of insulin dosage with prevention of renal failure may be due to either a renal protective effect of insulin or reduced insulin requirements secondary to either increased glucose removal in patients receiving continuous renal replacement therapy or reduced insulin clearance in renal failure.

In 2003, the results were published of a 6-month, prospective, single center, observational study evaluating glucose control and mortality risk in 523 adult patients in the ICU.[49] The goals of the study were to determine whether control of glucose metabolism or the degree of insulin administration was most likely to influence patient outcome and if there is a threshold glucose level above which there is an increased risk of death. Patients were predominantly male (72.8%) with a mean age of 64 years. Most subjects were cardiac surgery patients (85.1%), with a small subset of medical patients (11.7%).

Investigators defined six different bands of glycemic control and determined the amount of time each patient spent within each band. Blood glucose results were stratified based on ICU survival. Results showed that increased administration of insulin was positively and significantly associated with increased mortality. The authors concluded that glucose control rather than administration of exogenous insulin is the predominant factor in realizing decreased mortality. Furthermore, they observed a threshold blood glucose level between 145 and 180 mg/dl above which an increased risk of mortality exists. The authors suggest that a target blood glucose level of less than 145 mg/dl may be adequate and should be associated with less risk of hypoglycemia. The results of this study must be interpreted with caution because of its noninterventional design.

In 2003, results of a retrospective study were published in which the effect of hyperglycemia in a heterogeneous patient population was evaluated.[48] The study, which involved 1826 critically ill medical and surgical patients, found that increased mean serum glucose concentrations were associated with an increased mortality rate. Even modest increases in mean serum glucose concentration were associated with an increased rate of mortality. Due to its retrospective nature, this study did not allow for definitive conclusions regarding the effects of hyperglycemia. However, it provided compelling evidence for further studies into the role of hyperglycemia in causing an increased risk of mortality in a heterogeneous population.[52]

In a subsequent study, the same author evaluated the effect of a glucose management protocol in 800 patients compared with a historic control group of 800 patients.[50] The blood glucose goal was 140 mg/dl or less, and the study population included surgical and medical critically ill patients. Results showed that use of the glucose protocol led to significant decreases in hospital mortality (29.3%, p=0.002), new-onset renal failure (75%, p=0.03), patients requiring blood transfusions (18.7%, p=0.04), and ICU length of stay (10.8%, p=0.01). Despite its nonrandomized and historic control design, this study is important in showing mortality benefit in a heterogeneous critically ill population.

Unlike the previously mentioned 2001 study,[20] this study[50] showed no decrease in the frequency of infections. The author suggested that failure to decrease the frequency of infection may have been because the infection rate in the baseline period was already low owing to multiple

interventional policies such as antibiotic-impregnated catheters, universal infection precautions, and procedures for prevention of ventilator-associated pneumonia (e.g., head of bed elevation). However, the level of blood glucose control needs to be considered. The mean blood glucose level in the latter study[52] was 130.7 mg/dl compared with the mean morning glucose level of 103 mg/dl in the former[20] study. Post hoc analysis of the former study[20] showed that although intermediate glucose control (110–150 mg/dl) was associated with decreased mortality, it appeared that the benefits of decreased morbidity, including prevention of infections, required stricter glycemic control.[26]

Although the latter study[50] did not achieve the same reduction in mortality as that of the former[20] (29% vs 34%), the benefits of an insulin infusion protocol outside of a clinical trial were demonstrated. In addition, episodes of hypoglycemia (blood glucose level < 40 mg/dl) in the treatment groups occurred with greater frequency in the former study[20] (5.2%) than in the latter study[50] (0.34%). However, neither study reported clinically significant adverse outcomes in patients who developed hypoglycemia.

Insulin Effect on Pathophysiology of Hyperglycemia-Related Cellular Derangements

Arguing for the benefit of exogenous insulin administration, one group of authors showed that intensive insulin therapy exerts a powerful antiinflammatory effect through modulation of C-reactive protein and appears to counter the effects of low levels of mannose-binding lectin (MBL).[53] C-reactive protein and MBL are acute-phase proteins synthesized by the liver. C-reactive protein is used as an inflammatory marker, which may be involved in the activation of leukocytes and the complement system; MBL is involved in innate immunity by initiating opsonization of microorganisms. Deficiency in MBL has been associated with increased risk of infection.

The investigators conducted a post hoc analysis of the subset of patients (> 5 days in the ICU) in whom the mortality benefit of intensive insulin therapy occurred.[53] Serum C-reactive protein and MBL were measured on admission, days 5 and 15, and the last day of ICU stay. Baseline serum C-reactive protein and MBL concentrations were similar between the two treatment groups. Serum C-reactive protein concentrations were significantly suppressed at all time points in the intensive insulin therapy group and, after day 5, were independently associated with decreased mortality ($p<0.0001$) and decreased frequency of acute renal failure ($p<0.02$) by multivariate analysis. Also, conventional insulin therapy and a high baseline C-reactive protein significantly and independently increased the risk for prolonged inflammation and prolonged antibiotic therapy. For all patients, nonsurvivors tended to have lower baseline MBL concentrations compared with that of survivors.

In addition, a subanalysis of 243 conventionally treated patients showed that baseline MBL concentrations were significantly lower in nonsurvivors compared with survivors (387 vs 897 μg/ml, $p=0.04$).[53] During ICU stay, all patients had significant increases in MBL concentrations. Although intensive insulin therapy blunted increases in MBL concentrations compared with conventional insulin therapy ($p<0.02$), multivariate analysis showed that insulin therapy, not baseline MBL concentrations nor suppressed MBL concentrations over time, determined patient outcome. The authors suggested that the antiinflammatory activity associated with intensive insulin therapy partly explains the improvement in morbidity and mortality and that the possible adverse consequences of low baseline MBL levels are overcome. Further, results showed that the suppression of C-reactive protein was present among uninfected survivors, thus suggesting a direct antiinflammatory effect in the intensive insulin therapy group. However, the relative contributions of glycemic control versus insulin exposure are unknown.

The antiinflammatory effect of insulin has been suggested also through the suppression of proinflammatory cytokine and superoxide radical production and signaling.[26–28] Furthermore, postulated positive effects of insulin in critical illness include its role in the functional improvement of the insulin-sensitive organs through direct anabolic effect in acute illness, thus promoting tissue repair and preventing transfusions, dialysis, and critical illness polyneuropathy[21, 24, 26, 29]; enhanced energy production and delivery to ischemic tissues; decreased free radical production and enhanced nitric acid production; direct anabolic effects on muscles; and maintenance of macrophage and neutrophil function.[28]

Hyperglycemia and Infection in Patients Receiving Parenteral Nutrition

Although adequate nutrition is essential to

maintain a competent immune system,[54] overfeeding and inappropriate use of parenteral nutrition leads to serious complications.[55] Compared with enterally fed patients, patients who receive parenteral nutrition have a higher frequency of infectious complications, which include catheter-related sepsis, intraabdominal abscess, wound infections, and pneumonia.[56, 57] The increase in infection rate is likely the result of several factors, including catheter-related infections,[58] reduced intestinal integrity and immunity during bowel rest leading to bacterial translocation,[59] and the higher frequency of hyperglycemia with parenteral nutrition.[60] Patients receiving parenteral nutrition commonly have a higher frequency of hyperglycemia and more severe cases than those of enterally fed patients, and this usually necessitates higher insulin doses to achieve normoglycemia.[20, 56]

The Veteran Affairs Cooperative Study that evaluated the role of perioperative parenteral nutrition found that the benefits of this type of nutrition are mostly in severely malnourished patient.[60] A higher frequency of postoperative infections such as pneumonia and wound infections occurred in mildly malnourished patients compared with the severely malnourished patients who received parenteral nutrition. Although parenteral nutrition was beneficial in malnourished patients in reducing noninfectious complications, there was no change in infectious complications. A much higher frequency of severe hyperglycemia (serum glucose concentrations > 300 mg/dl) occurred in patients receiving parenteral nutrition (20%) compared with the control group (1%). Infection was 2.2 times more common in surgical patients who received parenteral nutrition. It was presumed that severe hyperglycemia in patients who received parenteral nutrition may have contributed to increased infectious complications.[61]

In a meta-analysis of enteral feeding versus parenteral nutrition studies in perioperative patients, 61% greater infectious complications were found in the parenteral nutrition group compared with those who received enteral nutrition.[62] Serum glucose concentrations were significantly higher in the parenteral nutrition group at all points of the analysis compared with the enteral nutrition group. Although these two publications[60, 62] pointed at a possible correlation between hyperglycemia and infection in patients receiving parenteral nutrition, the relationship between the timing of hyperglycemia and infection and the threshold of serum glucose concentration above which there is a higher infectious risk were not determined. Because hyperglycemia may represent a response to sepsis rather than necessarily being a cause of septic complications, the cause-effect relationship between hyperglycemia and infection in critically ill patients regardless of the route of nutrition support has been a debatable subject.[63]

Management of Hyperglycemia

Prevention

Prevention should be the first step in the management of hyperglycemia. In patients receiving parenteral nutrition, the best approach is to eliminate all other dextrose sources and start with a low dextrose load and advance slowly. A starting dextrose infusion rate at approximately 2 mg/kg/minute (significant suppression of glucose production occurs at 1–2 mg/kg/min[64]) should be advanced to a goal of 4 mg/kg/minute or less. These goals for dextrose administration are derived from several clinical trials that examined the optimum dextrose infusion rate to achieve the best patient outcomes.[65, 66]

In 1979, results were published of a study of convalescing burn patients in whom the authors evaluated the effect of increasing rates of exogenous glucose delivery on energy production while monitoring total carbon dioxide production, protein synthesis, and amount of insulin required to keep glucose toward normal range.[65] They found that there was a maximal rate of glucose infusion beyond which physiologically significant increases in protein synthesis and direct oxidation of glucose cannot be expected. Carbon dioxide production from glucose oxidation reached a plateau at greater than 5 mg/kg/minute, insulin did not increase glucose oxidation, and no significant difference was noted with protein synthesis among high (4.7–6.8 mg/kg/min), very high (7–9.3 mg/kg/min), and low (1.4–4.5 mg/kg/min) glucose infusions. Furthermore, if the optimum glucose infusion rate was exceeded, an increase occurred in the rate of carbon dioxide production from fat synthesis, resulting in large lipid deposits in the liver.

In 1980, another group studied the correlation between glucose clearance and glucose oxidation during administration of parenteral nutrition in a small population of postoperative nearly healthy subjects.[66] They showed no significant increase in blood glucose level when the dextrose infusion rate was increased from 4 to 7–9 mg/kg/minute. However, there was a limit to the ability to derive

energy from infused glucose and thus a questionable benefit derived from a dextrose infusion rate of 6–7 mg/kg/minute with potential detrimental effects of glucose overdose.

A retrospective study was performed to determine whether the frequency of hyperglycemia (blood glucose level > 200 mg/dl) increased in patients not predisposed to hyperglycemia who received parenteral nutrition in excess of 4–5 mg/kg/minute.[67] Results showed a positive correlation between parenteral nutrition dextrose infusion rate and blood glucose level; thus, the authors concluded that exceeding a dextrose infusion rate of 4–5 mg/kg/minute increases the risk of hyperglycemia.

Substituting a portion of the dextrose calories with lipids in parenteral nutrition helps control the hyperglycemia. Normally, 20–30% of total daily calories are provided as lipids. Increasing lipid intake beyond these levels to substitute for dextrose calories may not be desirable. This is due to concerns of possible fat immunosuppressive effects through reduction of cytokine secretion and inhibition of phagocytosis.[68] In addition, insulin therapy should be started as necessary for glucose control.

Historically, in a patient with hyperglycemia who is receiving parenteral nutrition (blood glucose target 150–200 mg/dl), sliding scale insulin would be started for 1–2 days, then the average of the 24-hour insulin requirements would be calculated; 70% of that would be included in the parenteral nutrition bag (with no less than 10 U/bag) while continuing to monitor insulin requirements and adjusting accordingly. However, using subcutaneous sliding scale insulin therapy may leave patients hyperglycemic for prolonged periods of time. Also, adding insulin to parenteral nutrition does not allow flexible titration of the insulin dosage based on blood glucose levels. As such, maintaining tight glucose control in hyperglycemic critically ill patients is best achieved with continuous insulin infusion.

In 1987, one group evaluated the efficacy, safety, and cost-effectiveness of treating parenteral nutrition–induced hyperglycemia with a continuous insulin infusion separate from the parenteral nutrition and showed that it was a safe, effective, cost-effective and more flexible way of controlling parenteral nutrition–induced hyperglycemia.[69]

After publication of the 2001 study,[20] there is less tolerance for hyperglycemia, and continuous insulin infusion is preferred over sliding scale insulin.

Insulin Infusions

As data continue to accumulate, the role of continuous insulin infusions in the ICU will likely be increasing. Available evidence supports the use of strict glycemic control in surgical patients, although published guidelines vary regarding selection of patients and level of glycemic control.[70, 71] Use of an algorithm provides an easy mechanism for improved glycemic control in patients in the ICU (Table 2). Any algorithm for glucose control should have a degree of flexibility to accommodate the clinical condition of each patient. Numerous factors contribute to a patient's hyperglycemia and the corresponding insulin requirements for control, including insulin production reserves, insulin sensitivity, caloric intake, severity of illness, presence of infection, and use of certain drugs (e.g., corticosteroids).[72] Insulin dosage adjustments should be proportionate to the rate of change of serum glucose concentration. Thus, a serum glucose concentration of 250 mg/dl may or may not require a change in the insulin dosage, depending on the preceding glucose concentration. Further, it should be expected that after normoglycemia is achieved, the need for monitoring glucose and adjusting the insulin dosage remains. As patients improve (or deteriorate), insulin sensitivity is expected to change, leading to changes in insulin requirements. Finally, insulin infusions should be interrupted whenever nutrition support is interrupted.

Use of continuous insulin infusions enables rapid glycemic control. However, more intensive monitoring is required to minimize risk of hypoglycemia, thus potentially straining personnel resources. As institutions move to adopt some form of intensive insulin therapy for critically ill patients, the level of glycemic control in the context of existing resources must be carefully evaluated. However, apart from reducing sepsis-related mortality, the dramatic reduction in morbidity associated with intensive insulin therapy should be fully appreciated. For example, intensive insulin therapy decreased the frequency of new-onset renal failure requiring dialysis by 41%.[20] Generally, patients receiving continuous renal replacement therapy require 1:1 nursing care. Thus, the decreased frequency of renal failure associated with intensive insulin therapy would be associated with significant resource savings. A full cost-benefit analysis seems warranted.

Although the safety and efficacy of insulin

Table 2. Algorithm for Insulin Dosing to Achieve Normoglycemia in the Intensive Care Unit

Blood Glucose Level (mg/dl)	Action or Adjustment	Frequency of Monitoring Blood Glucose Level
On admission to ICU		
> 220	Start insulin infusion 2–4 U/hr	
110–220	Start insulin infusion 1–2 U/hr	
< 110	Do not start insulin infusion	Every 4 hrs
During insulin infusion		
> 140	Increase insulin infusion by 1–2 U/hr	Every 1–2 hrs until in normal range
110–140	Increase insulin infusion by 0.5–1 U/hr	Every 1–2 hrs until in normal range
Approaching normal range	Adjust insulin dosage by 0.1–0.5 U/hr	Every 1–2 hrs until in normal range
Normal range	No change	Every 4 hrs
60–80	Reduce insulin dosage	Recheck within 1 hr
40–60	Stop insulin infusion, ensure adequate baseline glucose intake	Recheck within 1 hr
< 40	Stop insulin infusion, ensure adequate baseline glucose intake, administer glucose 10-g intravenous boluses	Recheck within 1 hr
Steeply falling	Reduce insulin dosage by one half	Every hr

ICU = intensive care unit.
The algorithm is designed for patients receiving enteral and/or parenteral nutrition. Dosage adjustments are a guide; any change in insulin dosage requires due consideration of magnitude of change in blood glucose level and rate of insulin infusion.
Adapted from reference 72.

nomograms had been demonstrated[73] before publication of the 2001 study,[20] the frequency of hypoglycemia in critically ill patients had not been described at the goal blood glucose level of 80–110 mg/dl. In the 2001 study,[20] patients received a mean insulin infusion rate of 0.04 IU/kg/hour with a mean dextrose administration rate of 9 g/hour. Hypoglycemia, defined as a blood glucose level below 40 mg/dl, occurred more in the intensive treatment group than in the conventional group (5.2% vs 0.8%). The authors noted that the episodes of hypoglycemia were largely a result of human error, which could be avoided with increased experience. Furthermore, none of the hypoglycemic episodes that occurred led to serious adverse events.[20, 26]

Conclusion

Available evidence has established the risk of morbidity and mortality secondary to infection related to hyperglycemia. Hyperglycemia results in impaired host defenses, increasing the risk for infection in the critically ill. Use of intensive insulin therapy has been shown to significantly decrease infectious complications in selected patient populations, perhaps through modulation of inflammatory mediators and minimization of impairment of host defense mechanisms. Further research will refine those patient populations that are most likely to benefit from intensive insulin therapy.

References

1. **The UK Prospective Diabetes Study (UKPDS) Group**. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
2. **The Diabetes Control and Complications Trial Research Group**. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
3. **Malmberg KA, Ryden LE, Efendic S**. Feasibility of insulin-glucose infusion in diabetic patients with acute myocardial infarction. Diabetes Care 1994;17:1007–14.
4. **Malmberg KA, Ryden LE, Efendic S, et al**. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57–65.
5. **Malmberg KA, Ryden LE, Hamsten A, Herlitz J, Waldenström A, Wedel H**. Effects of insulin treatment on cause-specific mortality and morbidity in diabetic patients with acute myocardial infarction. Eur Heart J 1996;17:1337–44.
6. **Malmberg KA**. Prospective randomized study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with diabetes mellitus. BMJ 1997;314:1512–15.
7. **Fietsam R, Bassett J, Glover JL**. Complications of coronary artery surgery in diabetic patients. Am Surg 1991;57:551–7.
8. **Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A**. Glucose control lowers the risk of wound infection in diabetics after open-heart operations. Ann Thorac Surg

1997;63:356–61.
9. **Pomposelli JJ, Baxter JK, Babineau TJ, et al**. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. J Parenter Enteral Nutr 1998;22: 77–81.
10. **Golden SH, Peart-Vigilance C, Kao WHL, Brancati FL**. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. Diabetes Care 1999;22:1408–14.
11. **Furnary AP, Zerr KJ, Grunkemeier GL, Starr A**. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg 1999;67:352–62.
12. **Trick WE, Scheckler WE, Tokars JE, et al**. Modifiable risk factors associated with deep sternal site infection after coronary artery bypass grafting. J Thorac Cardiovasc Surg 2000;119:108–14.
13. **Trick WE, Scheckler WE, Tokars JE, et al**. Risk factors for radial artery harvest site infection following coronary artery bypass graft surgery. Clin Infect Dis 2000;30:270–5.
14. **Latham R, Lancaster AD, Covington JF, Pirolo JS, Thomas CS**. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. Infect Control Hosp Epidemiol 2001;22:607–12.
15. **Guvener M, Pasaoglu I, Demircin M, Oc M**. Perioperative hyperglycemia is a strong correlate of postoperative infection in type II diabetic patients after coronary artery bypass grafting. Endocr J 2002;49:531–7.
16. **Estrada CA, Young JA, Nifong LW, Chitwood WR**. Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. Ann Thorac Surg 2003;75:1932–9.
17. **McCowen KC, Malhotra A, Bistrian BR**. Endocrine and metabolic dysfunction syndromes in the critically ill: stress-induced hyperglycemia. Crit Care Clin 2001;17:107–24.
18. **McMahon MM**. What to do about hyperglycemia in hospitalized patients. Nutr Clin Pract 1997;12:35–41.
19. **Mesotten D, van den Berghe G**. Clinical potential of insulin therapy in critically ill patients. Drugs 2003;63:625–36.
20. **van den Berghe G, Wouters P, Weekers F, et al**. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67.
21. **Knapke CM, Owens JP, Mirtallo JM**. Management of glucose abnormalities in patients receiving total parenteral nutrition. Clin Pharm 1989;8:136–44.
22. **Mizock BA**. Alterations in fuel metabolism in critical illness: hyperglycemia. Best Pract Res Clin Endocrinol Metab 2001;15:533–51.
23. **Wolfe RR**. Carbohydrate metabolism in critically ill patients: implications for nutritional support. Crit Care Clin 1987;3:11–24.
24. **Montori VM, Bistrian BR, McMahon MM**. Hyperglycemia in acutely ill patients. JAMA 2002;288:2167–9.
25. **van den Berghe G**. Beyond diabetes: saving lives with insulin in the ICU. Int J Obes 2002;3:S3–8.
26. **van den Berghe G, Wouters PJ, Bouillon R, et al**. Outcome benefit of intensive insulin therapy in critically ill patients: insulin dose versus glycemic control. Crit Care Med 2003;31:359–66.
27. **Weekers F, Giulietti A, Michalaki M, et al**. Metabolic, endocrine, and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness. Endocrinology 2003;144:5329–38.
28. **Groeneveld ABJ, Beinshuizen A, Visser FC**. Insulin: a wonder drug in the critically ill? Crit Care 2002;6:102–5.
29. **Dhatariya K**. Hyperglycemia in acute illness [letter]. JAMA 2003;289:1244.
30. **The ESICM Working Group**. Metabolic basis of nutrition in intensive care unit patients: ten critical questions. Intensive Care Med 2002;28:1512–20.
31. **Khaodhiar L, McCowen K, Bistrian B**. Perioperative hyperglycemia, infection or risk? Curr Opin Clin Nutr Metab Care 1999;2:79–82.
32. **The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus**. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997;20:1183–97.
33. **Rossini AA**. Why control blood glucose levels? Arch Surg 1976;111:229–33.
34. **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;125:1007–21.
35. **Perner A, Nielsen SE, Rask-Madsen J**. High glucose impairs superoxide production from isolated blood neutrophils. Intensive Care Med 2003;29:642–5.
36. **Kwoun MO, Ling PR, Lydon E, et al**. Immunologic effects of acute hyperglycemia in non-diabetic rats. J Parenter Enteral Nutr 1997;21:91–5.
37. **Black CT, Hennessey PJ, Andrassy RJ**. Short-term hyperglycemia depresses immunity through nonenzymatic glycosylation of circulating immunoglobulin. J Trauma 1998;30:830–2.
38. **Van Oss CJ, Border JR**. Influence of intermittent hyperglycemic glucose levels on the phagocytosis of microorganisms by human granulocytes in vitro. Immunol Commun 1978;7:669–76.
39. **Wheat LJ**. Infection and diabetes mellitus. Diabetes Care 1980;3:187–97.
40. **Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, Smith HL**. Infection and diabetes: the case for glucose control. Am J Med 1982;72:439–50.
41. **Alexiewicz JM, Kumar D, Smogorzewski M, Klin M, Massry SG**. Polymorphonuclear leukocytes in non–insulin-dependent diabetes mellitus: abnormalities in metabolism and function. Ann Intern Med 1995;123:919–24.
42. **Bagdade JD, Root RK, Bulger RJ**. Impaired leukocyte function in patients with poorly controlled diabetes. Diabetes 1974;23:9–15.
43. **Wilson RM**. Neutrophil function in diabetes. Diabet Med 1986;3:509–12.
44. **Sima AA, O'Neill SJ, Naimark D, Yagihashi S, Klass D**. Bacterial phagocytosis and intracellular killing by alveolar macrophages in BB rats. Diabetes 1988;37:544–9.
45. **Masuda M, Murakami T, Egawa H, Murata K**. Decreased fluidity of polymorphonuclear leukocyte membrane in streptozocin-induced diabetic rats. Diabetes 1990;39:466–70.
46. **MacRury SM, Gemmell CG, Patterson KR, MacCuish AC**. Changes in phagocytic function with glycemic control in diabetic patients. J Clin Pathol 1989;42:1143–7.
47. **Kjersem H, Hilsted J, Madsbad S, Wandall JH, Johansen KS, Borregaard N**. Polymorphonuclear leucocyte dysfunction during short term metabolic changes from normo- to hyperglycemia in type I (insulin dependent) diabetic patients. Infection 1988;16:215–21.
48. **Krinsley JS**. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003;78:1471–8.
49. **Finney SJ, Zekveld C, Elia A, Evans TW**. Glucose control and mortality in critically ill patients. JAMA 2003;290:2041–7.
50. **Krinsley JS**. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004;79:992–1000.
51. **Bistrian BR**. Hyperglycemia and infection: which is the chicken and which is the egg? J Parenter Enteral Nutr 2001;25:180–1.
52. **Coursin DB**. How sweet is euglycemia in critically ill patients? [editorial]. Mayo Clin Proc 2003;78:1460–2.
53. **Hansen TK, Thiel S, Wouters PJ, Christiansen JS, van den Berghe G**. Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. J Clin Endocrinol Metab 2003;88:1082–8.
54. **Chandra RK, Sarchielli P**. Nutritional status and immune responses. Clin Lab Med 1993;13:455–61.
55. **Klein CJ, Stanek GS, Wiles CE**. Overfeeding macronutrients to critically ill adults: metabolic complications. J Am Diet Assoc

1998;98:795–806.
56. **Moore FA, Moore EE, Jones TN, et al**. TEN versus TPN following major abdominal trauma reduced septic morbidity. J Trauma 1989;29:916–23.
57. **Kudsk KA, Croce MA, Fabian TC, et al**. Enteral versus parenteral feeding. Ann Surg 1992;215:503–13.
58. **Widmer AF**. Management of catheter–related bacteremia and fungemia in patients on total parenteral nutrition. Nutrition 1997;3(suppl 4):S18–25.
59. **Alverdy JC, Aoys E, Moss GS**. Total parenteral nutrition promotes bacterial translocation from the gut. Surgery 1988;104:185–90.
60. **The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group**. Perioperative total parenteral nutrition in surgical patients. N Engl J Med 1991;325:525–32.
61. **Pomposelli JJ, Bistrian BR**. Is total parenteral nutrition immunosuppressive? New Horiz 1994;2:224–9.
62. **Moore FA, Feliciano DV, Andrassy RJ, et al**. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. Ann Surg 1992;216:172–83.
63. **Kudsk KA, Lauledеrkind A, Hanna KM**. Most infectious complications in parenterally fed trauma patients are not due to elevated blood glucose levels. J Parenter Enteral Nutr 2001;25:174–9.
64. **Wolfe RR, Allsop JR, Burke JF**. Glucose metabolism in man: responses to intravenous glucose infusion. Metabolism 1979;28:210–20.
65. **Burke JF, Wolfe RR, Mullany CJ, Mathews DE, Bier DM**. Glucose requirements following burn injury. Ann Surg 1979;190:274–85.
66. **Wolfe RR, O'Donnell TF, Stone MD, Richmand DA, Burke JF**. Investigation of factors determining the optimal glucose infusion rate in total parenteral nutrition. Metabolism 1980;29:892–900.
67. **Rosmarin DK, Wardlaw GM, Mirtallo J**. Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. Nutr Clin Pract 1996;11:151–6.
68. **Seidner DL, Mascioli EA, Istfan NW, et al**. Effects of long-chain triglyceride emulsions on reticuloendothelial system function in humans. J Parenter Enteral Nutr 1989;13:614–19.
69. **Sajbel TA, Butro MP, Radway PR**. Use of separate insulin infusions with total parenteral nutrition. J Parenter Enteral Nutr 1987;11:97–9.
70. **Dellinger RP, Carlet JM, Masur H**. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858–73.
71. **Garber AJ, Moghissi ES, Bransome ED Jr, et al**. American College of Endocrinology position statement on inpatient diabetes and metabolic control. Endocr Pract 2004;10(suppl 2):4–9.
72. **van den Berhge G**. Insulin therapy for the critically ill. Clin Cornerstone 2003;5:56–63.
73. **Brown G, Dodek P**. Intravenous insulin nomogram improves blood glucose control in critically ill. Crit Care Med 2001;29:1714–19.