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Abstract

Background: Hyperglycemia is a frequent occurrence in adult hospitalized patients who receive nutrition support. Both hyperglycemia and hypoglycemia (resulting from attempts to correct hyperglycemia) are associated with adverse outcomes in diabetic as well as nondiabetic patients. This American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Clinical Guideline summarizes the most current evidence and provides guidelines for the desired blood glucose goal range in hospitalized patients receiving nutrition support, the definition of hypoglycemia, and the rationale for use of diabetes-specific enteral formulas in hospitalized patients. **Method:** A systematic review of the best available evidence to answer a series of questions regarding glucose control in adults receiving parenteral or enteral nutrition was undertaken and evaluated using concepts adopted from the Grading of Recommendations, Assessment, Development and Evaluation working group. A consensus process was used to develop the clinical guideline recommendations prior to external and internal review and approval by the A.S.P.E.N. Board of Directors. **Results/Conclusions:** 1. What is the desired blood glucose goal range in adult hospitalized patients receiving nutrition support? We recommend a target blood glucose goal range of 140–180 mg/dL (7.8–10 mmol/L). (Strong) 2. How is hypoglycemia defined in adult hospitalized patients receiving nutrition support? We recommend that hypoglycemia be defined as a blood glucose concentration of <70 mg/dL (<3.9 mmol/L). (Strong) 3. Should diabetes-specific enteral formulas be used for adult hospitalized patients with hyperglycemia? We cannot make a recommendation at this time. (Further research needed) (*JPEN J Parenter Enteral Nutr.* 2013;37:23-36)

Keywords

hyperglycemia; endocrinology; diabetes

Background

Hyperglycemia is a frequent occurrence in hospitalized patients who receive nutrition support. A survey of 126 U.S. hospitals found that the prevalence of hyperglycemia (blood glucose >180 mg/dL [10 mmol/L]) was 46% in the intensive care unit (ICU) and 32% in non-ICU areas.¹ Both hyperglycemia and hypoglycemia are associated with adverse outcomes in patients with diabetes mellitus as well as nondiabetic patients.^{1,2} Numerous trials have been conducted to investigate whether tight control of blood glucose affects outcomes, and the results have been inconsistent. Differences among studies may relate in part to timing of initiating nutrition, route of nutrition administration, caloric provision, glycemic target, and methods of blood glucose testing. This American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Clinical Guideline summarizes the most current evidence and provides guidelines for the desired blood glucose goal range in hospitalized patients receiving nutrition support, the definition of hypoglycemia, and the rationale for use of diabetes-specific enteral formulas in hospitalized patients. This guideline does not address other specific strategies for managing hyperglycemia in patients receiving nutrition support, as there are little to no data to support clinical practice recommendations in this area.

Methodology

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an organization composed of healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of clinical nutrition and metabolism. A.S.P.E.N. vigorously works to support quality patient care, education, and research

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in the fields of nutrition and metabolic support in all healthcare settings. These Clinical Guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. The A.S.P.E.N. Board of Directors has been publishing Clinical Guidelines since 1986.³⁻¹⁴ A.S.P.E.N. evaluates in an ongoing process when individual Clinical Guidelines should be updated.

These A.S.P.E.N. Clinical Guidelines are based on general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Because guidelines cannot account for every variation in circumstances, the practitioner must always exercise professional judgment in their application. These Clinical Guidelines are intended to supplement, but not replace, professional training and judgment.

A.S.P.E.N. Clinical Guidelines have adopted concepts of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group.¹⁵⁻¹⁷ A full description of the methodology has been published.¹⁸ Briefly, specific clinical questions where nutrition support is a relevant mode of therapy are developed and key clinical outcomes are identified. A rigorous search of the published literature is conducted, each included study assessed for research quality, tables of findings developed, the body of evidence for the question evaluated, and a recommendation for clinical practice that is based on both the best available evidence and the risks and benefits to patients developed by consensus. Recommendations are graded as strong when the evidence is strong and/or net benefits outweigh harms. Weak recommendations may be based on weaker evidence and/or important trade-offs to the patient. When limited research is available to answer a question, no recommendation can be made.

Results

For the current Clinical Guideline, inclusion criteria of adult subjects, complication of hyperglycemia, and hospital setting were used. The questions are summarized in Table 1. Search terms of *diabetes mellitus*, *hyperglycemia*, *hypoglycemia*, *clinical outcomes*, *parenteral nutrition*, and *enteral nutrition* were applied in various combinations to CENTRAL (The Cochrane Library), MEDLINE, EMBASE, Science Citation Index Expanded, LILACS, and CINAHL (until December 2011).

Question 1. What is the desired blood glucose goal range in adult hospitalized patients receiving nutrition support (Tables 2 and 3)?

Recommendation: We recommend a target blood glucose goal range of 140–180 mg/dL (7.8–10 mmol/L).

Grade: Strong

Rationale: Hyperglycemia is associated with increased mortality in hospitalized patients, both in the ICU¹⁹ and the non-ICU setting.²⁰ No clinical trials have been specifically designed to determine the effect of different blood glucose targets in adult hospitalized patients receiving nutrition support on clinical outcomes.

Earlier studies²¹⁻²³ showed that management of hyperglycemia with an insulin infusion in the ICU was associated with a reduction in mortality, leading a consensus conference to recommend that blood glucose concentrations in hospitalized patients be maintained below 110 mg/dL (6.1 mmol/L).³⁴ However, more recent large clinical trials failed to show benefit when such an aggressive target was achieved.^{25,27-31,35} The largest randomized controlled trial that used primarily enteral nutrition at levels of energy intake that were appropriate actually found a higher mortality in patients treated with intensive treatment compared with those treated to a target blood glucose range of 140–180 mg/dL (7.8–10 mmol/L).³¹ The explanation for these disparate results is

Table 1. Nutrition Support Clinical Guideline Recommendations in Adult Hospitalized Patients With Hyperglycemia.

| Question | Recommendation | Grade |
|--|--|-------------------------|
| What is the desired blood glucose goal range in adult hospitalized patients receiving nutrition support? | We recommend a target blood glucose goal range of 140–180 mg/dL (7.8–10 mmol/L). | Strong |
| How is hypoglycemia defined in adult hospitalized patients receiving nutrition support? | We recommend that hypoglycemia be defined as a blood concentration of <70 mg/dL (<3.9 mmol/L). | Strong |
| Should diabetes-specific enteral formulas be used for adult hospitalized patients with hyperglycemia? | We cannot make a recommendation at this time. | Further research needed |

not entirely clear, but hypoglycemia associated with aggressive treatment in the more recent studies is one likely explanation. It is apparent that mild to moderate hypoglycemia (40–70 mg/dL; 2.2–3.9 mmol/L) is not innocuous but rather is associated with adverse outcomes. No trials have compared a broader target glycemic range with a lower limit, for example, 110–180 mg/dL (6.1–10.0 mmol/L), to intensive treatment. Because of these findings, we recommend that the target blood glucose concentration in the critically ill adult should be 140–180 mg/dL (7.8–10 mmol/L). No randomized controlled trials have been conducted in non-ICU patients. This recommendation is consistent with those of the American Association of Clinical Endocrinologists, the American Diabetes Association,³⁶ and the Endocrine Society.³⁷

Question 2. How is hypoglycemia defined in adult hospitalized patients receiving nutrition support (Tables 4 and 5)?

Recommendation: We recommend that hypoglycemia be defined as a blood glucose concentration of <70 mg/dL (<3.9 mmol/L).

Grade: Strong

Rationale: Hypoglycemia is associated with adverse outcomes in hospitalized patients.^{25,38,39,40-54} Hypoglycemia could be partly responsible for the adverse effects noted with intensive insulin therapy, including mortality.²⁵ A large retrospective analysis of hypoglycemia in ICUs showed a stepwise and significant increase in mortality with increasingly severe hypoglycemia.³⁸ This recommendation carries a strong recommendation grade based on our assessment of the significant risk to the patient of hypoglycemia in the context of tight glucose control.

Symptoms of hypoglycemia can be missed in hospitalized patients who are sedated or ventilated, or with impaired sensorium. The American Diabetes Association Workgroup on Hypoglycemia and the American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control define hypoglycemia as any blood glucose <70 mg/dL (<3.9 mmol/L).³⁶ This value is the accepted definition in ambulatory patients and is a level at which counterregulatory hormone release (including sympathoadrenal activation) occurs. It is reasonable to apply the definition

of hypoglycemia in ambulatory patients to hospitalized patients. Antecedent hypoglycemia of this level can reduce the secretion of counterregulatory hormones resulting in impaired responsiveness to subsequent hypoglycemia.⁵⁵⁻⁵⁷ While some studies have defined hypoglycemia in critically ill patients as <40 mg/dL (<2.2 mmol/L), that threshold is lower than the level at which cognitive impairment can occur and is therefore not safe. In addition, a variety of point-of-care testing methods for blood glucose are used in hospitalized patients. The accuracy and precision of blood glucose monitoring devices is relatively poor, especially at low glucose concentrations.^{14,58} Using a blood glucose threshold of 70 mg/dL (3.9 mmol/L) instead of a lower value offers the additional benefit of a safety buffer to accommodate such testing errors. Regardless of the definition threshold of hypoglycemia, patients with symptoms of hypoglycemia at a higher level than 70 mg/dL (3.9 mmol/L) may require treatment for symptoms of hypoglycemia.

Question 3. Should diabetes-specific enteral formulas be used for hospitalized patients with hyperglycemia (Tables 6 and 7)?

Recommendation: We cannot make a recommendation at this time.

Grade: Further research needed

Rationale: The availability of enteral formulas with lower carbohydrate and higher monounsaturated fat content (compared with standard formulas commonly used in clinical settings) and with or without added fiber has prompted studies examining the effects on glycemic control. Additionally, most trials are short-term or single-meal studies, use oral nutrition supplements, or were conducted in long-term care facilities, rehabilitation, or other outpatient settings, limiting their application to hospitalized patients requiring enteral nutrition.

The trials that evaluated disease-specific formulas in patients requiring long-term nutrition support used glycemic or lipid control as their primary outcomes, as they were not sufficiently powered to detect differences in morbidity and/or mortality.^{59,60} The impact on glycemic and lipid control was inconclusive. Additional research is required.

Table 2. Evidence Table Question 1: What Is the Desired Glucose Goal Range in Adult Hospitalized Patients Receiving Nutrition Support?

| Author (ref #) | Study Design, Quality | Population, Setting, N | Study Objective | Primary End Points | Results | Comments |
|-----------------------------------|------------------------------------|---|---|--|---|--|
| Van den Bergh, 2001 ²¹ | RCT, unblinded, single center | Surgical ICU patients (N = 1548) | Compared tight glycemic control (target ≤ 110 mg/dL; 6.1 mmol/L) to less stringent control (180–200 mg/dL; 10–11.1 mmol/L) | In-hospital mortality | 34% reduction in in-hospital mortality with tight glycemic control ($P < .04$) | Used blood gas machine, which has superior accuracy and precision to other point-of-care devices, for glucose measurements; majority received PN and may have been overfed |
| Furnary, 2003 ²² | Historical controls, single center | Post-CABG (N = 3554) | Compared tight glycemic control (variable target) to less stringent control (< 200 mg/dL; 11.1 mmol/L) | In-hospital mortality | 53% reduction in in-hospital mortality with tight glycemic control ($P = .002$) | Few patients received nutrition support; point-of-care glucose measurements |
| Krinsley, 2004 ²³ | Historical controls, single center | Medical-surgical ICU (N = 1600) | Compared tight glycemic control (target ≤ 140 mg/dL; 7.8 mmol/L) to less stringent control (“usual care”) | In-hospital mortality | 29% reduction in in-hospital mortality with tight glycemic control ($P = .002$) | Mode of feeding was almost entirely enteral; point-of-care glucose measurements |
| Cheung, 2005 ²⁴ | Retrospective chart review | Hospitalized patients fed with PN (N = 109) | Evaluated association of hyperglycemia during PN on clinical outcomes | In-hospital mortality; cardiac, renal, infectious outcomes while fed with PN | Hyperglycemia of > 164 mg/dL (9.1 mmol/L) in patients receiving PN was associated with increased mortality compared with those with blood glucose < 124 mg/dL (6.9 mmol/L) (OR, 10.9; 95% CI, 2.0–60.5; $P < .01$); blood glucose of > 142 mg/dL fed with PN was associated with increased risk of all complications | Retrospective design |

(continued)

Table 2. (continued)

| Author (ref #) | Study Design, Quality | Population, Setting, N | Study Objective | Primary End Points | Results | Comments |
|------------------------------------|--|--|---|--|---|--|
| Van den Berghe, 2006 ²⁵ | RCT, unblinded, single center | Medical ICU patients (N = 1200) | Compared tight glycemic control (target ≤ 110 mg/dL; 6.1 mmol/L) to less stringent control (180–200 mg/dL; 10–11.1 mmol/L) | In-hospital mortality | No difference in mortality between groups treated with intensive vs conventional insulin | Patients fed via parenteral and enteral routes; arterial glucose sampling and point-of-care devices for glucose analysis |
| Lin, 2007 ²⁶ | Retrospective chart review | Hospitalized patients fed with PN (N = 457) | Evaluated the association between hyperglycemia and outcomes in patients fed with PN | In-hospital mortality | Mortality risk increased significantly with increasing degree of hyperglycemia during PN use compared with patients with glucose < 114 mg/dL (6.3 mmol/L) | Retrospective design |
| Brunkhorst, 2008 ²⁷ | RCT, 2-by-2 factorial design, unblinded, multicenter | Medical-surgical ICU patients with severe sepsis or septic shock (N = 537) | Compared tight glycemic control (target ≤ 110 mg/dL; 6.1 mmol/L) to less stringent control (180–200 mg/dL; 10.0–11.1 mmol/L) | 28-day mortality and morbidity (mean SOFA) | No difference in mortality and mean SOFA scores were similar between groups treated with intensive vs conventional insulin | Intensive insulin therapy arm terminated early due to high frequency of hypoglycemia; mode of feeding was shared between enteral and parenteral routes; point-of-care or arterial glucose measurements |
| De La Rosa, 2008 ²⁸ | RCT, unblinded, single center | Medical-surgical ICU (N = 504) | Compared tight glycemic control (target ≤ 110 mg/dL; 6.1 mmol/L) to less stringent control (180–200 mg/dL; 10–11.1 mmol/L) | 28-day mortality | No difference in mortality between groups treated with intensive vs conventional insulin | Majority of patients received EN; arterial glucose sampling and point-of-care devices for glucose analysis |
| Arabi, 2008 ²⁹ | RCT, unblinded, single center | Medical-surgical ICU (N = 523) | Compared tight glycemic control (target ≤ 110 mg/dL; 6.1 mmol/L) to less stringent control (180–200 mg/dL; 10–11.1 mmol/L) | ICU mortality | No difference in mortality between groups treated with intensive vs conventional insulin | Majority of patients received EN; arterial glucose sampling and point-of-care devices for glucose analysis |

(continued)

Table 2. (continued)

| Author (ref #) | Study Design, Quality | Population, Setting, N | Study Objective | Primary End Points | Results | Comments |
|--------------------------------|-----------------------------|---|---|--|---|--|
| Preiser, 2009 ³⁰ | RCT, unblinded, multicenter | Medical-surgical ICU patients (N = 1078) | Compared tight glycemic control (target ≤ 110 mg/dL; 6.1 mmol/L) to less stringent control (140–180 mg/dL; 7.8–10.0 mmol/L) | ICU mortality | No difference in mortality between patients treated with intensive vs conventional insulin | Study was terminated early due to protocol violations and therefore was underpowered; majority received EN and were not overfed; arterial glucose sampling or point-of-care glucose measurements |
| NICE-SUGAR, 2009 ³¹ | RCT, unblinded, multicenter | Medical-surgical ICU patients (N = 6104) | Compared tight glycemic control (target ≤ 108 mg/dL; 6.0 mmol/L) to less stringent control (140–180 mg/dL; 7.8–10.0 mmol/L) | 90-day all-cause mortality | Mortality was 10.1% higher in the intensive insulin arm of the study ($P = .02$) | Majority received EN and were not overfed; used both blood gas analysis and point-of-care devices for glucose analysis |
| Pasquel, 2010 ² | Retrospective chart review | Hospitalized patients fed with PN (N = 276) | Evaluated clinical predictive capability of the glycemic response to PN | Hospital length of stay, hospital complications, mortality | Blood glucose within 24 hours of PN initiation of > 180 mg/dL (10 mmol/L) was associated with increased mortality (OR, 2.8; 95% CI, 1.2–6.8; $P = .020$) and increased risk of pneumonia (OR, 3.1; 95% CI, 1.4–7.1) and acute renal failure (OR, 2.3; 95% CI, 1.1–5.0) | Retrospective design |
| Sarkisian, 2010 ³² | Retrospective chart review | Non-critically ill inpatients fed with PN (N = 100) | Determined the association of PN use with hyperglycemia (> 180 mg/dL; 10.0 mmol/L) and the association of hyperglycemia on healthcare outcomes | Acute coronary events, renal failure, infection, hospital length of stay, ICU admission, sepsis, and mortality | Hyperglycemia in patients receiving PN was associated with increased mortality (OR, 7.22; 95% CI, 1.08–48.29; $P = .042$) | Retrospective design; small study population (only 17/100 patients had hyperglycemia) |

(continued)

Table 2. (continued)

| Author (ref #) | Study Design, Quality | Population, Setting, N | Study Objective | Primary End Points | Results | Comments |
|-------------------------|----------------------------|--|---|---|---|--|
| Lee, 2011 ³³ | Retrospective chart review | Medical ICU, fed with PN without history of diabetes mellitus (N = 88) | Determined effect of PN dextrose provision on hyperglycemia (≥ 140 mg/dL; 7.8 mmol/L) and clinical outcomes | Relationship between hyperglycemia and complications (infectious, renal, cardiac) and mortality | Patients who were hyperglycemic received more dextrose from PN; hyperglycemia was associated with increased mortality compared to patients fed with PN with normoglycemia (42.4% vs 12.8%, $P = .008$) | Retrospective design, small study population |

CABG, coronary artery bypass graft; CI, confidence interval; EN, enteral nutrition; ICU, intensive care unit; NICE-SUGAR, Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation; OR, odds ratio; PN, parenteral nutrition; RCT, randomized controlled trial; SOFA, Sequential Organ Failure Assessment; VISEP, Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis.

Table 3. GRADE Table Question 1: What Is the Desired Glucose Goal Range in Adult Hospitalized Patients Receiving Nutrition Support?

| Comparison | Outcome | Quantity, Type Evidence | Findings | GRADE of Evidence for Outcome | Overall Recommendation GRADE |
|-----------------------------------|-----------|---|---|-------------------------------|------------------------------|
| Tight vs standard glucose control | Mortality | 7 RCTs, ^{21,25,27-31} 2 historical control trials, ^{22,23} 5 retrospective reviews ^{2,24,26,32,33} | Tight glycaemic control was better in 1 RCT ²¹ and 2 historical control trials, ^{22,23} no different in 5 RCTs, ^{25,27-30} and worse in the largest RCT ³¹ ; 5 retrospective reviews suggest harm with PN-associated hyperglycemia ^{2,24,26,32,33} | Moderate | Strong |

PN, parenteral nutrition; RCT, randomized controlled trial.

Table 4. Evidence Table Question 2: How Is Hypoglycemia Defined in Adult Hospitalized Patients Receiving Nutrition Support?

| Author (ref #) | Study Design, Quality | Population, Setting, N | Study Objective | Primary End Points | Results | Comments |
|--------------------------------|-----------------------------|--|--|--------------------|--|---|
| Boucai, 2011 ⁴⁰ | Retrospective record review | Hospitalized patients, not in ICU, with at least 1 blood glucose <70 mg/dL (3.9 mmol/L), N = 3349 of 31,970 total admissions | Evaluate mortality risk associated with hypoglycemia | Mortality | Hypoglycemia (HR, 1.67; 95% CI, 1.33–2.09; <i>P</i> < 0.001) In patients with spontaneous hypoglycemia (HR, 2.72; 95% CI, 1.97–3.47; <i>P</i> < .001) After adjustment for comorbidities, relationship no longer significant In patients with insulin-induced hypoglycemia (HR, 1.06; 95% CI, 0.74–1.52) | Hypoglycemia may be a marker of disease rather than a direct cause of death |
| Chi, 2011 ⁴¹ | Retrospective record review | Consecutive admissions to shock/trauma ICU, N = 3125 | Examine the impact of glycemic states on mortality; hypoglycemia as blood glucose ≤60 mg/dL | Mortality | Hypoglycemia increased actual risk beyond predicted and in dose-response fashion | |
| D'Ancona 2011 ⁴² | Retrospective record review | Consecutive cardiac surgery patients, N = 596 | Examine impact of hyperglycemia (blood glucose >180 mg/dL) and hypoglycemia (blood glucose <70 mg/dL (3.9 mmol/L) on clinical outcomes | Mortality | Hypoglycemia (OR, 20.0; 95% CI, 2.9–136.9; <i>P</i> = .002) | |
| Hermanides, 2010 ⁴³ | Retrospective record review | Medical ICU, N = 2168 Cardiothoracic surgical ICU, N = 3560 | Evaluate impact of blood glucose variability vs mortality; hypoglycemia as blood glucose ≤45 mg/dL | Mortality | High glucose variability may be more important than hypoglycemia alone in predicting mortality | |

(continued)

Table 4. (continued)

| Author (ref #) | Study Design, Quality | Population, Setting, N | Study Objective | Primary End Points | Results | Comments |
|-------------------------------|-----------------------------|---|---|--|---|---|
| Krinsley, 2011 ⁴⁴ | Retrospective record review | ICU patients from 6 hospitals, N = 6240 | Assess mortality risk of blood glucose <70 mg/dL (3.9 mmol/L) | Mortality | Glucose <70 mg/dL (3.9 mmol/L); (RR, 1.78; 95% CI, 1.39–2.27, <i>P</i> < .0001) Glucose 40–69 mg/dL; (RR, 1.29; 95% CI, 1.11–1.51, <i>P</i> = .0011) Glucose <40 mg/dL; (RR, 1.87; 95% CI, 1.46–2.40, <i>P</i> < .0001) | Dose-response relationship with mortality risk vs level of hypoglycemia |
| Mortensen, 2010 ⁴⁵ | Retrospective record review | Patients admitted with pneumonia; hypoglycemia as blood glucose <70 mg/dL (3.9 mmol/L), N = 787 | Examine whether hypoglycemia as <70 mg/dL (3.9 mmol/L) is associated with increased 30-day mortality, after adjusting for potential confounders | Mortality | Hypoglycemia (adjusted OR, 4.1; 95% CI, 1.4–11.7) | |
| Siegelaar, 2010 ⁴⁶ | Retrospective record review | Medical, surgical ICU patients, N = 5828 | Examine impact of intensive insulin therapy to achieve glycemic target of 70–125 mg/dL (4–7 mmol/L) | Mortality | Mean glucose ≤6.6 mmol/L (OR, 2.4; 95% CI, 1.4–4, <i>P</i> = .002) in medical patients Mean glucose ≤6.9 mmol/L (OR, 4.9; 95% CI, 1.2–21.6, <i>P</i> = .03) in surgical patients | |
| Stamou, 2011 ⁴⁷ | Retrospective record review | Consecutive cardiac surgery patients, N = 2538 | Identify risk factors for hypoglycemia during intensive insulin therapy Examine their impact on surgical mortality | Hypoglycemia as blood glucose <60 mg/dL (3.3 mmol/L) | Hypoglycemia independent predictor (OR, 2.7; 95% CI, 1.1–6.3, <i>P</i> = .027) | |

(continued)

Table 4. (continued)

| Author (ref #) | Study Design, Quality | Population, Setting, N | Study Objective | Primary End Points | Results | Comments |
|-------------------------------|---|--|---|--------------------|--|---|
| Durao, 2010 ⁴⁸ | Retrospective record review | ICU admissions assigned to target blood glucose 4.4–6.1 mmol/L vs 4.4–8 mmol/L, N = 130 Hypoglycemia as blood glucose <3.3 mmol/L | Evaluate mortality associated with 2 glucose control regimens | Mortality | Hypoglycemia (OR, 2.9; 95% CI, 1.21–7.41) | Small sample, randomization not mentioned |
| Egi, 2010 ³⁸ | Retrospective record review | Patients admitted to ICU who also had hypoglycemia, N = 1109 | Evaluate impact of mild (glucose 72–81 mg/dL) or moderate (glucose <71 mg/dL) hypoglycemia on mortality | Mortality | Both hospital and ICU mortality OR increased dose-dependently with lower levels of hypoglycemia | |
| Arabi, 2009 ⁴⁹ | Retrospective record review of nested cohort within RCT | Medical-surgical ICU patients, N = 523 | Determine whether factors for hypoglycemia as blood glucose ≤40 mg/dL (2.2 mmol/L); assess impact on mortality | ICU mortality | Adjusted for confounders, hypoglycemia not significantly associated with increased mortality (HR, 1.31; 95% CI, 0.7–2.46) | Relatively small sample size, no power analysis |
| Kosiborod, 2009 ⁵⁰ | Retrospective record review | Patients hospitalized with acute MI and hyperglycemia, N = 7820 | Determine whether mortality risk associated with hypoglycemia is similar in patients who develop hypoglycemia spontaneously and those who develop it as a result of insulin therapy | Mortality | Hypoglycemia in patients who were not treated with insulin vs normoglycemic patients (OR, 2.32; 95% CI, 1.31–4.12) No difference in hypoglycemia treated with insulin vs normoglycemic patients (OR, 0.92; 95% CI, 0.58–1.45) | Authors attribute hypoglycemia risk to more severe critical illness, not to insulin |

(continued)

Table 4. (continued)

| Author (ref #) | Study Design, Quality | Population, Setting, N | Study Objective | Primary End Points | Results | Comments |
|------------------------------|---|--|--|--------------------------------|---|--|
| Turchin, 2009 ⁵¹ | Retrospective record review | Patients with diabetes admitted to non-ICU area, N = 4368 admissions of 2582 patients | Determine whether hypoglycemic episodes as blood glucose \leq 50 mg/dL (2.8 mmol/L) are associated with higher mortality in diabetic patients hospitalized in the general ward | Inpatient and 1-year mortality | Odds of inpatient death rose 3-fold for every 10-mg/dL decrease in the lowest blood glucose during hospitalization ($P = .0058$) Mortality at 1 year not impacted | Patients treated with PN excluded from analysis |
| Bagshaw, 2009 ⁵² | Retrospective record review | Consecutive admissions to ICU, N = 66,184 | Examine impact of early hypoglycemia as blood glucose $<$ 80 mg/dL (4.5 mmol/L) | Mortality | Hypoglycemia vs ICU mortality (OR, 1.41; 95% CI, 1.31–1.54) Hypoglycemia vs hospital mortality (OR, 1.36; 95% CI, 1.27–1.46) Mortality higher with lower levels of hypoglycemia | |
| Kaukonen, 2009 ⁵³ | Retrospective record review | Consecutive admissions to ICU, N = 1124 | Examine incidence of hypoglycemia as blood glucose $<$ 72 mg/dL (4 mmol/L) and impact on mortality | Mortality | Hypoglycemia vs no hypoglycemia, 24% vs 14.7%, $P = .11$ | Small sample size (n = 25 patients with hypoglycemia) limits power |
| Krinsley, 2007 ⁵⁴ | Retrospective record review with case control | Consecutive patients admitted to medical, surgical, or cardiac ICU, N = 5372; patients with severe hypoglycemia, N = 102 | Determine risk factors for development of severe hypoglycemia defined as glucose $<$ 40 mg/dL (2.2 mmol/L) in critically ill patients and define the outcomes of this complication | Mortality | Severe hypoglycemia independent predictor of mortality (OR, 2.28; 95% CI, 1.41–3.70; $P = .0008$) | |

CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; MI, myocardial infarction; OR, odds ratio; PN, parenteral nutrition; RCT, randomized controlled trial; RR, relative risk.

Table 5. GRADE Table Question 2: What Glucose Range Should Define Hypoglycemia?

| Comparison | Outcome | Quantity, Type Evidence | Findings | GRADE of Evidence for Outcome | Overall Recommendation GRADE |
|-------------------------------|-----------|----------------------------|--|-------------------------------|------------------------------|
| Normoglycemia vs hypoglycemia | Mortality | 16 OBS ^{38,40-54} | 14 Increased risk, ^{40-48,50,52,54} 2 no difference ^{49,53} | Low | Strong |

OBS, observational study.

Table 6. Evidence Table Question 3: Should Diabetes-Specific Enteral Formulas Be Used for Adult Hospitalized Patients With Hyperglycemia?

| Author (ref #) | Study Design, Quality | Population, Setting, N | Study Objective | Primary End Points | Results | Comments |
|-------------------------------|-----------------------|---|---|--|---|---|
| Leon-Sanz, 2005 ⁵⁹ | RCT, unblinded | Hospitalized with head/neck cancer or neurologic disorder and with type 2 diabetes mellitus (N = 104) | Compared 2 diabetes-specific formulas (high CHO from starch and sucrose vs low CHO/high MUFA) | Blood glucose level, triglyceride level, daily insulin requirement | No significant difference in glucose, triglycerides, or insulin requirements | No standard enteral formula comparison; analysis conducted only in patients who fulfilled energy intake goal and completed 2 weeks of treatment (32 of 104 patients randomized) |
| Mesejo, 2005 ⁶⁰ | RCT, single blinded | Intensive care unit; stress hyperglycemia or diabetes mellitus type 1 or 2 (N = 50) | Compared high protein/high MUFA + fiber vs high protein control EN | Glycemic control, insulin requirement | Significant improvement in glycemic control: 176.8 ± 44.0 vs 222.8 ± 47.1 mg/dL (P = .001) Significant improvement in median insulin requirement at 14 days: 8.7 (2.3–27.5) vs 30.2 (21.5–51.7) U/d (P = .001) | Included patients with and without diabetes mellitus |

CHO, carbohydrate; EN, enteral nutrition; MUFA, mono-unsaturated fatty acid; RCT, randomized controlled trial.

Table 7. GRADE Table Question 3: Should Diabetes-Specific Enteral Formulas Be Used for Adult Hospitalized Patients With Hyperglycemia?

| Comparison | Outcome | Quantity, Type Evidence | Findings | GRADE of Evidence for Outcome | Overall Recommendation GRADE |
|------------------------------|---------------------|-------------------------|---|-------------------------------|------------------------------|
| Diabetes formula vs standard | Glycemic control | 2 RCTs ^{59,60} | 1 No difference, ⁵⁹ 1 improved ⁶⁰ | Low | Further research needed |
| | Insulin requirement | 2 RCTs ^{59,60} | 1 No difference, ⁵⁹ 1 improved ⁶⁰ | Low | |

RCT, randomized controlled trial.

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Erratum

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