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A.S.P.E.N. Clinical Guidelines: Nutrition Support of Adult Patients With Hyperglycemia

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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 ICU[19] 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 studies[21-23] 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 Berghe, 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 or central venous 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 glycemic 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; $P < 0.001$) In patients with spontaneous hypoglycemia (HR, 2.72; 95% CI, 1.97–3.47; $P < .001$) 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; $P = .002$)	
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, P < .0001) Glucose 40–69 mg/dL; (RR, 1.29; 95% CI, 1.11–1.51, P = .0011) Glucose <40 mg/dL; (RR, 1.87; 95% CI, 1.46–2.40, P < .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, P = .002) in medical patients Mean glucose ≤6.9 mmol/L (OR, 4.9; 95% CI, 1.2–21.6, P = .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, P = .027)	

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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 predicting 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

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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 ≤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, 2003[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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A.S.P.E.N. Board of Directors Providing Final Approval

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