

Fluids, Electrolytes, Acid-Base Disorders, and Nutrition Support

Roland N. Dickerson, Pharm.D., FCCP, FCCM, FASHP, BCNSP

**University of Tennessee College of Pharmacy
Memphis, Tennessee**

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Learning Objectives

1. Appropriately assess hyponatremia and hypernatremia in a critically ill patient, and develop an appropriate treatment plan.
2. Discuss the causes and treatment of common intracellular electrolyte disorders.
3. Differentiate among the causative factors for metabolic acidosis and alkalosis, and construct a therapeutic treatment algorithm.
4. Specify the appropriate route (parenteral or enteral) of nutrition administration, amount of nutrients, and particular component formulation to be provided to a given critically ill patient.
5. Identify appropriate markers for assessing the tolerance, safety, and efficacy of enteral or parenteral nutrition therapy.
6. Describe methods for ensuring appropriate glycemic control in critically ill patients.
7. Identify pertinent drug-nutrient interactions, and provide recommendations for the safe and effective delivery of medications to patients receiving enteral or parenteral nutrition therapy.
8. Discuss current controversies in the initiation, management, and monitoring of nutrition therapy for the critically ill patient.

Abbreviations in This Chapter

ABG	Arterial blood gas
AG	Anion gap
AKI	Acute kidney injury
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
BEE	Basal energy expenditure
BG	Blood glucose
CKD	Chronic kidney disease
ECF	Extracellular fluid
EN	Enteral nutrition
GRV	Gastric residual volume
IBW	Ideal body weight
ICF	Intracellular fluid
ICU	Intensive care unit
LOS	Length of stay
NB	Nitrogen balance
NG	Nasogastric

PN	Parenteral nutrition
RCT	Randomized controlled trial
SIADH	Syndrome of inappropriate antidiuretic hormone
TBI	Traumatic brain injury
UUN	Urine urea nitrogen

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. Which is the most appropriate indication for parenteral nutrition (PN)?
 - A. Severe anorexia.
 - B. Lack of bowel sounds.
 - C. Ileus.
 - D. High gastric residual volume (GRV).
2. Which is the most appropriate replacement fluid for a patient with significant nasogastric (NG) fluid drainage?
 - A. 0.9% sodium chloride and potassium chloride 20 mEq/L.
 - B. 0.45% sodium chloride and potassium chloride 20 mEq/L.
 - C. 5% dextrose in 0.225% sodium chloride and potassium chloride 20 mEq/L.
 - D. Lactated Ringer solution.
3. Which trace mineral would best be increased for a PN-dependent patient with intractable diarrhea?
 - A. Zinc.
 - B. Copper.
 - C. Iodine.
 - D. Manganese.
4. A 70-year-old man admitted to the intensive care unit (ICU) for sepsis was recently given a diagnosis of syndrome of inappropriate antidiuresis. His serum sodium acutely fell from 130 mEq to 115 mEq/L during the past 3 days, and he recently seized secondarily to this problem. Which would be the most appropriate treatment option?
 - A. Intravenous 0.9% sodium chloride.
 - B. Intravenous DDAVP (desmopressin acetate).
 - C. Intravenous 3% sodium chloride.
 - D. Intravenous conivaptan.

5. Other than the absorption/infusion rate, which best explains why enteral potassium administration is safer than parenteral potassium administration?
 - A. Bioavailability of potassium is significantly lower with enteral versus parenteral administration.
 - B. Feed-forward sensing of changes in mesenteric potassium concentration increases urinary potassium excretion.
 - C. Potassium chloride elixir is likely to cause diarrhea and reduce potassium absorption.
 - D. Wax matrix tablets sequester potassium release throughout the gastrointestinal (GI) tract.
6. A 45-year-old woman with a history of celiac disease and alcoholism is admitted to the ICU. There is no evidence of significant acute or chronic blood loss. Her hematocrit is 30%, hemoglobin is 9 g/L, and mean corpuscular volume is 105 fL. Her serum methylmalonic acid concentration is within normal limits, and her serum homocysteine concentration is elevated. Serum ferritin is within normal limits. Which does this patient most likely have a deficiency of?
 - A. Iron.
 - B. Thiamine.
 - C. Folic acid.
 - D. Cyanocobalamin.
7. A 40-year-old man (weight 60 kg) is admitted to the trauma ICU after a motor vehicle accident. He is noted to have a serum magnesium concentration of 1.2 mg/dL, and his family states he has a history of alcohol abuse. He is given magnesium sulfate 6 g intravenously over 4 hours by the primary service. His repeat serum magnesium concentration on the following day is 1.8 mg/dL. Which would be the most appropriate treatment for this patient?
 - A. No treatment is necessary because his serum magnesium concentration is normal.
 - B. If a repeat serum magnesium concentration is 2 mg/dL or greater, no additional magnesium therapy is indicated.
 - C. Supplemental calcium therapy should be given concurrently with the magnesium therapy.
 - D. Additional magnesium therapy should be given daily over the next 4–5 days.
8. A 45-year-old man (weight 90 kg) admitted to the ICU after operative management of necrotizing pancreatitis is given PN consisting of 350 g of dextrose, 130 g of amino acids, and 90 g of lipid emulsion (20%) daily. A 24-hour urine collection for determining the nitrogen balance (NB) shows a urine urea concentration of 900 mg/dL for a urine output of 2700 mL. He received 100% of his PN solution, and there was no significant change in his blood urea nitrogen (BUN) during the NB study. Which most accurately depicts his NB?
 - A. -15 g/day.
 - B. -7.5 g/day.
 - C. -2.5 g/day.
 - D. +2.5 g/day.

I. FLUIDS AND ELECTROLYTES

A. General Overview

1. Body water compartments
 - a. Total body water (TBW): About 60% of body weight for males; about 55% of body weight for females; lower percentage for those who are obese and elderly (0.5 L/kg for males; 0.45 L/kg for females)
 - b. About 60% of TBW is intracellular.
 - c. About 40% of TBW is extracellular water (about 80% is interstitial fluid; about 20% plasma volume)
2. Estimating daily fluid requirements
 - a. 30–35 mL/kg (overestimates large person, underestimates small person)
 - b. 100 mL/kg for the first 10 kg, 50 mL/kg for the next 10 kg, and 20 mL/kg thereafter
 - c. Increased insensible losses with fever (around 10%–15% for every degree Celsius greater than 37°C)

Table 1. Effect of Body Temperature on Insensible Fluid Losses (Surgery 1968;64:154-64)

Rectal Temperature (°C)	No. of Patients	Mean Fluid Loss (mL/m ² /day)
36.7–37.7	205	552
37.8–38.2	160	600
38.3–38.8	48	768
38.9–40	14	840

3. Estimating electrolyte requirements
 - a. Approximate electrolyte concentrations in the extracellular and intracellular fluids (ECF and ICF) (Fluid, Electrolyte, and Acid-Base Disorders, Vol 1. New York: Churchill Livingstone, 1985:1-38.)

Table 2. Electrolyte Concentrations in the ECF and the ICF

Electrolyte	Extracellular Fluid (mEq/L)		Intracellular Fluid (mEq/L)
	(plasma)	(interstitial)	(muscle)
Sodium	140	145	12
Potassium	4.5	4.8	160
Chloride	104	117	2
Bicarbonate	24	27	10
Calcium	5.0	2.8	—
Magnesium	1.5	1.0	34
Phosphate	2	2.3	54

- b. “Normal” daily requirements

Table 3. “Normal” Daily Requirements

Sodium	50–100 mEq/day
Potassium	0.5–1.5 mEq/kg
Phosphorus	30–24 mmol
Magnesium	24–32 mEq
Calcium	10–20 mEq
Chloride ^a	80–120 mEq
Acetate ^a	80–120 mEq

^aDepending on the acid-base status of the patient.

- c. Approximate electrolyte content of GI fluids (in milliequivalents per liter) (About Surgery: A Clinical Approach. Philadelphia: Elsevier Health Sciences, 1996:5-17; Acta Chir Scand Suppl 1963;(suppl 306):301-65.

Table 4. Electrolyte Content of GI Fluids

Fluid	Average Daily Volume (mL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Magnesium (mEq/L)
Stomach	1000–2000	60–90	10–15	100–130	—	0.9
Duodenum	400–600	140	5–10	90–120	80	—
Small intestine	2000–2500	140	5–10	90–120	30–40	6–12
Colon	< 300	60	20–30	50	—	6–12
Pancreas	600–800	140	5–10	75	115	0.4
Bile	300–600	140	5–10	100	30	1.1

- d. Electrolyte composition of common intravenous solutions (in milliequivalents per liter)

Table 5. Electrolyte Composition of Common Intravenous Solutions

Solutions	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Calcium (mEq/L)	Magnesium (mEq/L)
5% dextrose in water	—	—	—	—	—	—
0.9% sodium chloride (normal saline)	154	—	154	—	—	—
0.45% sodium chloride (one-half normal saline)	77	—	77	—	—	—
5% dextrose in 0.225% sodium chloride (5% dextrose in one-fourth normal saline)	34	—	34	—	—	—
3% sodium chloride (hypertonic saline)	513	—	513	—	—	—
Lactated Ringer solution	130	4	109	28	2.7	—

4. Regulation of effective circulating volume
 - a. Kidney – Renin-angiotensin-aldosterone system
 - b. Extra-renal (carotid sinus, atrium) – Sympathetic nervous system (epinephrine and norepinephrine) and atrial natriuretic peptide

Table 6. Hemodynamic Assessment (<http://surgicalcriticalcare.net>)

Ejection Fraction	Adjusted End-Diastolic Volume Index for Normal Subjects	Adjusted End-Diastolic Volume Index for Critically Ill Patients
20	200	240
30	150	180
35	125	150
40	100	120
50	50	60

5. Regulation of plasma osmolality
 - a. Vasopressin release
 - b. Thirst
 - c. Osmoreceptor sensitivity

B. Water and Sodium Disorders

1. Dehydration: As evidenced by decreased urine output (unless patient has glycosuria or diuretic therapy), increased serum urea nitrogen/serum creatinine ratio (SUN/SCr greater than 20), insufficient net fluid balance “from nursing records), poor skin turgor, dry mucous membranes, orthostatic hypotension, “contraction alkalosis.” Increased losses
 - a. Fever
 - b. GI fluids
2. Volume excess: As evidenced by the presence of peripheral/sacral/pulmonary edema, anasarca, congestive heart failure, acute kidney injury (AKI)
 - a. Excessive fluid intake
 - b. Impaired ability to excrete excess water and sodium (e.g., heart failure, cirrhosis with ascites, renal failure)
3. Hyponatremia
 - a. Classic evaluation
 - i. Exclude hyperglycemia, mannitol, and glycine for unmeasured osmoles (hypertonic hyponatremia).
 - ii. Exclude factitious/pseudo-hypoglycemia (isotonic hyponatremia).
 - iii. Evaluate ECF volume (increased, normal, decreased).
 - iv. Consider use of urine sodium and osmolality, if necessary.
 - v. Consider patient conditions/diagnoses.
 - b. 2014 European Society of Endocrinology guidelines (Intensive Care Med 2014;40:320-31).
 - i. Exclude hyperglycemia and other causes of non-hypotonic hyponatremia.
 - ii. Evaluate urine sodium and osmolality.
 - iii. Assess ECF and arterial blood volume, diuretics, presence of kidney disease
 - c. Treatment of hyponatremia
 - i. Acute or severe symptoms? – Immediate treatment with hypertonic saline
 - ii. ECF expanded – Fluid and sodium restriction

- iii. ECF reduced and low urine sodium – Give sodium and fluids (treat etiologies if possible); reduce diuretic therapy.
- iv. ECF normal – Consider syndrome of inappropriate antidiuresis or secondary adrenal insufficiency – Fluid restriction first; consider conivaptan or tolvaptan; fluid restriction with use of 0.9% sodium chloride solution with or without diuretic therapy
- 4. Hyponatremia
 - a. Excessive sodium intake (hypertonic saline, 0.9% sodium chloride solution, lactated Ringer solution)
 - b. Dehydration

Patient Case

Questions 1–3 pertain to the following case.

A 55-year-old woman (70 kg) admitted to the ICU for pneumonia and respiratory failure develops a serum sodium of 125 mEq/L on her fifth day of hospital admission. Her other laboratory values include a serum potassium of 4.6 mEq/L, chloride 100 mEq/L, total carbon dioxide (CO₂) content 24 mEq/L, BUN 20 mg/dL, SCr 1.1 mg/dL, and glucose 167 mg/dL. She is currently receiving a 1-kcal/mL, 62-g/L enteral feeding formula at 60 mL/hour and a 5% dextrose in 0.45% sodium chloride infusion at 25 mL/hour. Her fluid balance has ranged from +300 to +600 mL/day during the past 3 days. She has no evidence of any significant amount of edema. Her measured serum osmolality is 265 mOsm/kg, urine osmolality is 490 mOsm/kg, and urine sodium is 67 mEq/L.

1. Which is the most likely etiology for the patient's hyponatremia?
 - A. Factitious hyponatremia.
 - B. Adrenal insufficiency.
 - C. Cerebral salt wasting.
 - D. Syndrome of inappropriate antidiuretic hormone (SIADH).
2. Which would be the most appropriate treatment for this woman?
 - A. Give sodium chloride tablets 1 g three times daily.
 - B. Limit fluids.
 - C. Change the intravenous fluid to 0.9% sodium chloride.
 - D. Provide a short-term intravenous infusion of 3% sodium chloride.
3. Which change in the enteral feeding formula would be best for this patient?
 - A. Add sodium chloride 100 mEq/L to the current formula.
 - B. Change the formula to a fish oil–enriched product.
 - C. Change the formula to a low-carbohydrate, high-fat product.
 - D. Change the formula to a 2-kcal/mL formula and decrease the rate.

C. Disorders of Potassium Homeostasis

1. Potassium homeostasis overview
 - a. 98% intracellular
 - b. Total body stores: 35–50 mEq/kg in normal healthy adults; 25–30 mEq/kg if significantly undernourished
 - c. Normal serum concentration: 3.5–5.2 mEq/L
 - d. Serum concentration can be influenced by changes in pH (for every 0.1 increase in arterial pH, serum potassium will decrease by around 0.6 mEq/L [range 0.4–1.3 mEq/L]) (J Clin Invest 1956;35:935-9), and vice versa.

- e. Average daily requirement: About 0.5–1.2 mEq/kg
 - f. Kidney is primary route of elimination.
 - g. Losses can be extensive with severe diarrhea or body fluid drainages (see Table 4).
 - h. Magnesium status can influence potassium homeostasis (Crit Care Med 1996;24:38-45; J Am Soc Nephrol. 2007;18:2649-52; Arch Intern Med 1992;152:40-5).
 - i. Magnesium serves as a cofactor for the Na-K-ATPase pump.
 - ii. Magnesium closes potassium channels in distal nephron.
2. Hypokalemia
- a. Definition: Serum potassium less than 3.5 mEq/L, though most ICUs prefer to keep patients at 4.0 mEq/L or greater, if possible
 - b. Signs and symptoms: Weakness, cramps, cardiac arrhythmias (ST depression, QT prolongation, flat T wave, U wave). If severe hypokalemia (e.g., serum potassium less than 2 mEq/L), flaccid paralysis, ileus
 - c. Etiologies:
 - i. Inadequate intake (rare; kidneys can usually adapt)
 - ii. Increased losses
 - (a) GI fluid losses (e.g., diarrhea, fistula, drainages)
 - (b) Hypomagnesemia
 - (c) Medications (diuretics, amphotericin B, mineralocorticoid excess, penicillins)
 - (d) Polyuria (diabetes insipidus)
 - (e) Renal potassium excretion (type I/distal and type II/proximal renal tubular acidosis)
 - (f) Diabetic ketoacidosis
 - iii. Increased requirements (building of new muscle/tissue – refeeding syndrome)
 - iv. Extracellular to intracellular shift
 - (a) Medications (β -adrenergic agonists, including albuterol, sodium bicarbonate or other alkalinizing agents; insulin)
 - (b) Acute alkalemia
 - (c) Hypothermia
 - (d) Pentobarbital/thiopental?
 - d. Estimating total body potassium deficit
 - i. Transtubular potassium gradient to assess the contribution of the kidney to the hypokalemia is no longer recommended because of the variability in urea reabsorption in the cortical collecting duct, which alters solute removal. Use spot urine potassium if kidney-based etiology of hypokalemia is unclear.
 - ii. Sterns equation (Medicine (Baltimore) 1981;60:339-54) (most commonly used method):
Potassium deficit (mEq) = $100 \times (4.4 - \text{serum potassium})$
 - iii. Segal equation (Core Concepts in the Disorders of Fluid, Electrolytes, and Acid-Base Balance. New York: Springer, 2013:49-102.)
(makes nonlinear assumption of deficit estimate): Potassium deficit (mEq per 70 kg):
 $3300 \times \exp(-\text{serum potassium}/1.5) - 200$
 - iv. Sterns equation (Medicine (Baltimore) 1981;60:339-54) adjusted to the extent of malnourishment:
Estimate total body potassium (mEq/kg) by:
Well nourished: 35–50 mEq/kg
Undernourished: 20–35 mEq/kg
Serum potassium of 3.0 mEq/L approximates a 10% total body deficit.
Serum potassium of 2.5 mEq/L approximates a 20% total body deficit.

- e. Treatment:
- Treat, alleviate, or reduce the potential etiologies for hypokalemia, if possible.
 - Ensure hypokalemia is not at least partly attributable to hypomagnesemia.
 - The estimated deficit should be replaced over 1–3 days (depending on the extent of deficit; the larger a deficit, the longer the repletion period) by giving boluses and increasing the potassium content in intravenous fluids and PN/enteral nutrition (EN) solutions.
 - Enteral or oral potassium replacement is the preferred and safer route of delivery because of the time of absorption and feed-forward regulation of potassium homeostasis. (Ann Intern Med 2009;150:619-25), administration of potassium chloride liquid directly into the small bowel (by a jejunal or duodenal feeding tube) should be avoided because of its osmolality, which can lead to abdominal cramping, distension, and diarrhea.
 - Short-term infusions of potassium chloride or potassium phosphate should be given only by central vein. Potassium chloride can be given at 20 mEq/hour if the patient has continuous electrocardiography (ECG) monitoring in the ICU. 10 mEq/hour is safest if the patient is asymptomatic or not in the ICU. Potassium chloride comes prepackaged as 20- and 40-mEq units in sterile water for injection. Peripheral intravenous solutions should not contain potassium chloride at more than 40–60 mEq/L in an effort to reduce the pain associated with the infusion of a concentrated potassium chloride solution and to prevent inappropriate rapid and excessive potassium chloride dosing.
 - Empiric intravenous potassium dosing. This algorithm (used by the Regional One Health Nutrition Support Service) is only a guide for critically ill patients and may need to be adjusted according to patient body size, renal function, and ongoing severity of losses.

Table 7. Empiric Intravenous Potassium Dosing

Serum Potassium (mEq/L)	Potassium Chloride Dosage (mEq) ^a	Laboratory Tests
3.5–3.9	40 mEq x 1; increase in IV/PN/EN	Obtain BMP, magnesium next AM
3–3.4	40 mEq x 2; increase in IV/PN/EN	Obtain BMP, magnesium next AM; may wish to get stat K 1–2 hours after second 40-mEq bolus, especially if losses are thought to be high. Reassess
2–2.9	40 mEq x 3+; increase in IV/PN/EN	Obtain repeat serum K 1–2 hours after second 40-mEq bolus and reassess; may need one or two additional boluses; repeat. Check serum magnesium next AM. Reassess

^aPotassium phosphate may be considered in lieu of potassium chloride if concurrent hypokalemia and hypophosphatemia (very common in critically ill patients receiving EN/PN). Thirty millimoles of potassium phosphate is equivalent to 44 mEq of K.

AM = morning; BMP = basic metabolic panel; IV = intravenous; K = potassium.

- The accuracy of the historical assumption of “a 0.5 to 0.6 mEq/L increase in serum potassium will occur for every 40 mEq of intravenous potassium administered” (Arch Intern Med 1990;150:613-7; J Clin Pharmacol 1994;34:1077-82)
- Serum potassium concentrations are equilibrated within 1–2 hours after completion of the intravenous potassium chloride infusion (Crit Care Med 1991;19:694-9; J Clin Pharmacol 1994;34:1077-82) and are recommended for patients with severe and/or complicated cases of hypokalemia.

3. Hyperkalemia

- a. Definition: Serum potassium greater than 5.2 mEq/L, although usually not a significant problem until serum potassium approaches 6 mEq/L
 - i. Rule out factitious hyperkalemia (hemolysis of blood sample, white blood cell count greater than 10×10^3 cells/mm³, platelet count greater than 400,000/mm³).
 - ii. Assess arterial blood gas (ABG) (severe acidosis).
 - iii. Immediately after a large blood transfusion?
- b. Signs and symptoms: Peaked and tented T waves on ECG, symptoms similar to those of hypokalemia (weakness, paralysis)
- c. Etiologies:
 - i. Drugs – Potassium-sparing diuretics (spironolactone, amiloride, triamterene), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, heparin, trimethoprim, octreotide
 - ii. Excessive intake (usually in combination with compromised renal function) – Be sure to examine all intravenous fluids, enteral and PN regimens, penicillin G (1.7 mEq of potassium per million units), packed red blood cells (potassium 7.5–13 mEq/L)
 - iii. Renal dysfunction (chronic kidney disease [CKD], AKI)
 - iv. Hyporeninemic hypoaldosteronism
 - v. Tissue catabolism (chemotherapy, rhabdomyolysis)
 - vi. Severe acidemia
 - vii. Elderly patients
- d. Treatment
 - i. Calcium gluconate (10%) 1- to 2-g intravenous slow push (especially if ECG changes) to stabilize the myocardium
 - ii. Regular human insulin 10 units intravenously plus or minus 50 g of dextrose intravenously (results in only temporary redistribution)
 - iii. Sodium bicarbonate 50–100 mEq intravenously (especially if acidemic – results in only temporary redistribution)
 - iv. Sodium polystyrene sulfonate 25–50 g (intragastric administration preferred) – Increases potassium elimination
 - v. Albuterol (results in only temporary redistribution)
 - vi. Loop diuretics – Increase potassium elimination
 - vii. Hemodialysis – Increases potassium elimination
 - viii. Make sure no exogenous sources of potassium (e.g., intravenous fluids, EN, PN); to reduce intake with EN or PN; use a “renal” (no or low-electrolyte formulation, if necessary)

D. Disorders of Magnesium Homeostasis

1. Magnesium homeostasis overview
 - a. 99% intracellular (17% of total body content is in the muscle) or in the skeleton
 - b. Total body stores: Around 2000 mEq
 - c. Normal serum concentration: 1.8–2.4 mg/dL (about 30% bound to protein)
 - d. Average daily requirement: Around 24–40 mEq/day
 - e. Kidney is primary route of elimination (around 70% reabsorbed in ascending loop of Henle) and is without any hormonal regulation of renal magnesium reabsorption.
 - f. Losses can be extensive with severe diarrhea or body fluid drainages (see Table 4).
 - g. Magnesium depletion can influence potassium and calcium homeostasis.

2. Hypomagnesemia

- a. Definition: Although the lower limit of normal for serum magnesium concentrations is 1.8 mg/dL (1.5 mEq/L), most clinicians define significant hypomagnesemia as 1.5 mg/dL (1.3 mEq/L) or less. Many ICUs have a target serum magnesium concentration greater than 2 mg/dL (1.8 mEq/L). Serum concentrations of magnesium may be slightly falsely lowered in the presence of significant hypoalbuminemia.
- b. Signs and symptoms: Muscle weakness, cramping, paresthesias, Chvostek and Trousseau signs, tetany, QT prolongation, hypokalemia, hypocalcemia
- c. Etiologies:
 - i. GI losses (especially diarrhea) – Average stool loss of about 6 mEq/L; up to 10–12 mEq/L or greater for secretory diarrheal losses
 - ii. Alcohol (increased renal excretion; impaired absorption; poor nutritional status of patients who abuse alcohol)
 - iii. Sepsis/critical illness (increased urinary excretion – several factors)
 - iv. Pancreatitis (partly attributable to calcium-magnesium soap formation in peritoneum)
 - v. Thermal injury/traumatic brain injury (TBI) (increased urinary excretion – several factors)
 - vi. Drugs – Diuretics, amphotericin B, cyclosporin/tacrolimus, foscarnet, pentamidine, cisplatin/carboplatin/ifosfamide/cetuximab, lactulose/orlistat, aminoglycosides (?), digoxin (?), proton pump inhibitors (?)
 - vii. Polyuria (osmotic agents, hypercalcemia, ureagenesis)
- d. Estimating magnesium deficit: For a serum magnesium concentration of less than 1.5 mg/dL (1.3 mEq/L), a 1- to 2-mEq/kg deficit can be expected.
- e. Treatment:
 - i. Treat the etiology (if possible).
 - ii. Successful treatment of hypomagnesemia usually takes 3–5 days of intravenous therapy. Intramuscular magnesium therapy for replacement therapy is inadvisable because of the limit on volume per injection site with respect to dosage requirements and tissue irritation.
 - iii. Intravenous magnesium sulfate 32–48 mEq/day (4–6 g/day) – Suggested to be sufficient to maintain serum magnesium within 2–2.5 mg/dL for most magnesium-deficient patients (Crit Care Med 1996;24:38-45; Annu Rev Med 1981;32:245-259).
 - iv. Empiric intravenous magnesium sulfate dosing. This algorithm (used by Regional One Health's Nutrition Support Service) (Nutrition 1997;13:303-8) was designed primarily for trauma and thermally injured patients but can likely be universally applied to other critically ill patient populations. The therapy may need to be adjusted according to renal function and ongoing severity of losses. Our empiric approach to dosing intracellular electrolytes for patients with significant renal impairment is to give one-half the recommended dose (see Table 7). However, electrolyte therapy for patients with renal impairment must be individualized according to individual response.

Table 8. Empiric Intravenous Magnesium Sulfate Dosing

Serum Magnesium (mg/dL)	Dose (g/kg)
1.6–1.8	0.05
1–1.5	0.1
< 1	0.15

For ease of use and preparation, intravenous magnesium sulfate should be ordered in 2 g units (e.g., 2 g, 4 g, 6 g). The drug should be mixed in 100–250 mL of normal saline or 5% dextrose and given at a rate no faster than 1 g (8 mEq) per hour (Nutrition 1997;13:303-8). Maximum dose should be held at a ceiling of 8–10 g per administration. Magnesium concentrations are often elevated for several hours or longer after an infusion because it takes about 48 hours for the magnesium to fully redistribute to the body tissues (Nutrition 1997;13:303-8)

- v. Oral magnesium: Difficult to successfully accomplish in critically ill patients because of the adverse GI effects of oral magnesium (e.g., diarrhea) and the high elemental magnesium doses required to achieve repletion. Although it has been inferred that certain oral magnesium products are better tolerated than others (e.g., gluconate vs. oxide), this tolerability likely pertains to the elemental magnesium content of the products. The lower the elemental magnesium content, the more tolerable the oral product. However, the lower the magnesium content, the more difficult it is to achieve magnesium repletion for a patient with significant magnesium depletion.

Table 9. Common Oral Magnesium Products

Salt Form	Strength (mg)	Elemental Mg Content (mEq)	Usual Dosing
Oxide	400	19.8	1–2 tablets twice or three times daily
	140	6.9	
Gluconate	500	2.2	1–2 tablets twice or three times daily
Chloride	100	2.6	1–2 tablets twice or three times daily

Mg = magnesium.

Table 10. Oral Magnesium Content

Salt Form	% Elemental Magnesium Content
Oxide	60
Carbonate	45
Hydroxide	42
Citrate	16
Lactate	12
Chloride	12
Sulfate	10
Gluconate	5

3. Hypermagnesemia
 - a. Definition: Serum magnesium concentration greater than 2.4 mg/dL; patients usually do not experience symptoms until the serum magnesium concentration exceeds about 4 mg/dL
 - b. Signs and symptoms: Hypotension, decreased deep tendon reflexes, cardiovascular manifestations (e.g., bradycardia, somnolence, muscle paralysis, arrhythmias) generally do not occur until serum concentrations are greater than 4 mg/dL
 - c. Etiologies: Renal failure or impairment early post-infusion elevation of serum magnesium concentration, excessive dosing of magnesium/antacids, post-cathartic use (e.g., magnesium citrate) – To develop hypermagnesemia, these events usually occur together with renal impairment.
 - d. Treatment:
 - i. Remove source of magnesium intake.
 - ii. Intermittent slow bolus doses of calcium gluconate (2 g) over 5–10 minutes until severe symptoms abate (the effect of calcium is transient, and repeat therapy may be needed as frequently as every hour)
 - iii. Ventilate the patient, if necessary.
 - iv. Hemodialysis

Patient Case

Questions 4 and 5 pertain to the following case.

A 55-year-old man (weight 70 kg) is admitted to the ICU after a total colectomy and hepatic resection for stage IV colon cancer. He has a history of an unintentional 20-lb weight loss during the past several months before hospital admission. He is a 2 pack/day tobacco smoker and has a history of frequent alcohol consumption. He is currently weaning from the ventilator; however, his NG volume output is greater than 2 L/day, and PN is initiated. The intent is to achieve goal caloric and protein intake within 3–4 days. His serum laboratory values are as follows: sodium 140 mEq/L, potassium 3.2 mEq/L, chloride 102 mEq/L, total CO₂ content 25 mEq/L, BUN 14 mg/dL, SCr 0.9 mg/dL, calcium 8.1 mg/dL, phosphorus 2 mg/dL, magnesium 1.4 mg/dL, and albumin 2.5 g/dL.

4. Which potassium-phosphorus dosing regimen would be most appropriate for this patient?
 - A. Potassium chloride liquid 40 mEq per NG tube for two doses, 2 Neutra-Phos capsules in water per NG tube.
 - B. Potassium phosphate 30 mmol intravenously x 1 dose, followed by two 40-mEq potassium chloride doses per NG tube.
 - C. Potassium chloride 40 mEq intravenously x 1 dose and potassium phosphate 45 mmol intravenously x 1 dose.
 - D. Potassium chloride 40 mEq intravenously x 1 dose and potassium phosphate 30 mmol intravenously x 1 dose.
5. In addition to potassium and phosphorus supplementation, the patient is given magnesium sulfate 6 g intravenously over 6 hours. His repeat serum magnesium the next day is 1.9 mg/dL. Which therapeutic option would be best for this patient?
 - A. Give magnesium oxide 500 mg twice daily for 4–5 days.
 - B. Give magnesium sulfate 2–4 g intravenously daily for 4–5 days.
 - C. Give a second dose of 6 g of magnesium sulfate intravenously.
 - D. No additional treatment is necessary.

E. Disorders of Calcium Homeostasis

1. Calcium homeostasis overview

- a. Most prevalent intracellular cation in body; 99% of body's calcium in bone; highly protein bound in plasma
- b. Total body stores: About 1–1.2 kg of calcium
- c. Normal serum concentration: 8.5–10.5 mg/dL; normal serum ionized concentration 1.12–1.32 mmol/L
- d. Serum concentration can be influenced by:
 - i. Changes in plasma albumin concentration – For every 1 g/dL in serum albumin below 4 g/dL, serum calcium will decrease by around 0.8 mg/dL (Clin Chim Acta 1971;35:483-9); do not use in critically ill patients (inaccurate) (JPEN J Parenter Enteral Nutr 2004;28:133-41). Use ionized calcium concentration for critically ill patients. However, most (85%) critically ill patients with a total serum calcium concentration less than 7 mg/dL are hypocalcemic (ionized serum calcium of 1.12 mmol/L or less) (Nutr Clin Pract 2007;22:323-8).
 - ii. Changes in pH (for every 0.1-unit increase in arterial pH, serum ionized calcium will decrease by about 0.05 mmol/L (Arch Pathol Lab Med 2002;126:947-50) because of increased protein binding
- e. Average daily requirement: 15 mEq/day intravenously with PN (Ann Surg 1983;197:1-6); 1–3 g/day orally
- f. Kidney is primary route of elimination.
- g. Magnesium status can influence calcium homeostasis.
 - i. Hypomagnesemia results in end-organ resistance to parathyroid hormone.
 - ii. Hypomagnesemia may impair parathyroid hormone secretion.
 - iii. Hypocalcemia will correct within 2 days after hypomagnesemia is corrected.

2. Hypocalcemia

- a. Definition: Corrected serum total calcium less than 8.5 mg/dL (non-ICU patients); ionized serum calcium concentration less than 1.12 mmol/L
- b. Signs and symptoms: Tingling, paresthesias, hyperactive deep tendon reflexes, Chvostek and Trousseau signs, prolonged QT interval
- c. Etiologies
 - i. Critical illness
 - ii. Continuous renal replacement therapy (CRRT) (citrate anticoagulation)
 - iii. Massive blood transfusion
 - iv. Hypomagnesemia
 - v. Hyperphosphatemia
 - vi. Pancreatitis
 - vii. Drugs (amphotericin B, cisplatin, cyclosporine, foscarnet, bisphosphonates, loop diuretics)
 - viii. Malabsorption
 - ix. Hypoparathyroidism
 - x. Chronic kidney injury/AKI
 - xi. Vitamin D deficiency
 - xii. Severe alkalemia
- d. Treatment: Regional One Health Nutrition Support Service intravenous calcium gluconate dosing guidelines (JPEN J Parenter Enteral Nutr 2005;29:436-4; JPEN J Parenter Enteral Nutr 2007;31:228-33; Nutrition 2007;23:9-15)

Table 11. Regional One Health Nutrition Support Service Intravenous Calcium Gluconate Dosing Guidelines

Ionized Calcium (mmol/L)	Intravenous Calcium Gluconate Dosage (mEq)
1–1.12	2 g (9.3 mEq) calcium gluconate in 100 mL of 0.9% NaCl or D ₅ W over 2 hours
≤ 0.99	4 g (18.6 mEq) calcium gluconate in 100 or 250 mL of 0.9% NaCl or D ₅ W over 4 hours

For ease of use and preparation, calcium gluconate should be ordered in gram increments. Calcium chloride should be used (preferably) only in code situations, not for routine replacement therapy, because the chloride salt contains about 2.5 times the amount of elemental calcium and can cause tissue necrosis when given peripherally in contrast to calcium gluconate. However, during extreme circumstances, such as a national drug shortage of intravenous calcium gluconate, calcium chloride can be given in 0.67- and 1.3-g doses in lieu of 2- and 4-g calcium gluconate doses. In addition, calcium chloride should never be added to the PN solution unless there is no phosphate in the PN solution and the commercial amino acids used in the PN solution do not contain phosphorus (some amino acid products do contain phosphate). A serum ionized calcium concentration determination should be repeated several hours after completing the calcium gluconate infusion to allow equilibration (Nutrition 2007;23:9-15). Therapy that is more aggressive may need to be considered for patients with tetany or life-threatening cardiac arrhythmias caused by hypocalcemia.

Intravenous calcium administration should be used with extreme caution in patients with severe hypokalemia or in those receiving digoxin or other digitalis alkaloids.

Always check the serum phosphorus concentration because hyperphosphatemia can induce hypocalcemia, given the metastatic precipitation of calcium phosphate in the soft tissues and lungs (usually associated with renal disease).

D5W = 5% dextrose in water; NaCl = sodium chloride.

Patient Case

Questions 6 and 7 pertain to the following case.

A 24-year-old man (weight 90 kg) is admitted to the trauma ICU postoperatively from repair of his duodenal, jejunal, ileal, and colon injuries, hepatorrhaphy, and splenectomy after several gunshot wounds to the abdomen. He also received 10 units of packed red blood cells. He is noted to have a serum ionized calcium concentration of 0.86 mmol/L, potassium of 4.6 mEq/L, and magnesium of 1.8 mg/dL. His SCr concentration is 0.8 mg/dL, and his urine output is greater than 0.5 mL/kg/hour.

6. Which is the most likely etiology for his hypocalcemia?
 - A. Hypomagnesemia.
 - B. Excessive urinary diuresis.
 - C. Blood transfusion.
 - D. Critical illness.
7. Which therapeutic regimen would be best for this patient?
 - A. Calcium gluconate 2 g intravenously over 2 hours.
 - B. Calcium gluconate 4 g intravenously over 4 hours.
 - C. Calcium chloride 1 g intravenous push over 5–10 minutes.
 - D. No calcium therapy necessary.

3. Hypercalcemia

- a. Definition: Corrected serum calcium greater than 10.5 mg/dL or ionized calcium greater than 1.32 mmol/L; signs and symptoms are more evident when total serum calcium of 12 mg/dL or greater or ionized calcium of 1.5 mmol/L or greater
- b. Signs and symptoms: Mental status changes, polyuria, shortened QT interval, bradycardia, atrioventricular block
- c. Etiologies:
 - i. Immobilization
 - ii. Chronic critical illness–associated metabolic bone disease

- iii. Excessive calcium intake
 - iv. Hyperparathyroidism
 - v. Granulomatous diseases (tuberculosis, sarcoidosis)
 - vi. Malignancy
 - vii. Drugs (thiazide diuretics, vitamin D)
 - viii. Dehydration
 - d. Treatment:
 - i. Mobilize the patient (if possible); discontinue calcium from the PN solution.
 - ii. Intravenous fluids with 0.9% sodium chloride (if dehydrated) at 200 to 300 mL/hour x 48 hours or until rehydrated with or without furosemide 40–80 mg intravenously every 12 hours
 - iii. Calcitonin 4 units/kg intramuscularly every 12 hours; can be increased to 8 units/kg every 12 hours as needed
 - iv. Pamidronate 90 mg intravenously once for acute hypercalcemia not related to etiologies i or ii
 - v. Pamidronate 30 mg intravenously daily for 3 days if hypercalcemia caused by etiologies i or ii
 - vi. This author's practice: Salmon calcitonin 200 units intramuscularly every 12 hours x 48 hours (rapid tachyphylaxis often limits therapy duration). Two hundred units is selected as the dosage because it comes from the manufacturer in a 200-IU/mL vial and is usually near the initial appropriate dosage range for many patients. If the patient is thought to have chronic critical illness–associated metabolic bone disease or hypercalcemia from immobilization, it is suggested to simultaneously add pamidronate 30 mg intravenously daily for 3 consecutive days because of the delay in bisphosphonate's onset of action (Chest.2000;118:761-6). Monitor for hypocalcemia. Do not use bisphosphonates in patients with renal impairment.
 - vii. Parathyroidectomy for patients with primary hyperparathyroidism
 - viii. Prednisone 40 mg/day and greater for 10 days for patients with granulomatous diseases (e.g., sarcoidosis, tuberculosis)
- F. Disorders of Phosphorus Homeostasis
- 1. Phosphorus homeostasis overview
 - a. 99% intracellular, of which 85% is bound to bone
 - b. Extracellular pool of phosphorus: Around 600 mg (about 20 mmol), 10% protein bound
 - c. Normal serum concentration: 2.5–4.5 mg/dL
 - d. Serum concentration can be influenced by parathyroid hormone (increased parathyroid hormone leads to increased urinary excretion of phosphorus), and alkalemia can decrease serum phosphorus concentration.
 - e. Average daily requirement: Around 20 mg/kg/day
 - f. Kidney is primary route of elimination.
 - 2. Hypophosphatemia
 - a. Definition: Serum phosphorus less than 2.5–3 mg/dL; severe hypophosphatemia less than 1–1.5 mg/dL
 - b. Signs and symptoms: Weakness, paresthesias; severe depletion can lead to congestive cardiomyopathy, cardiac arrest, seizures, coma, respiratory arrest, rhabdomyolysis
 - c. Etiologies:
 - i. Alcoholism
 - ii. Malnutrition/refeeding syndrome
 - iii. Critical illness (especially trauma, TBI, thermal injury)
 - iv. Diabetic ketoacidosis
 - v. Hepatic resection
 - vi. Drugs – Insulin, catecholamines, antacids, sucralfate, calcium

- vii. Alkalemia
- viii. Malabsorption – Chronic diarrhea
- ix. Hyperparathyroidism
- x. Cancer (phosphatonins [e.g., fibroblast growth factor-23])
- d. Treatment
 - i. Target serum phosphorus concentration when patient is in the ICU and ventilator-dependent: 4 mg/dL (N Engl J Med 1985;313:420-4; Inten Care Med 1995;21:826-31)
 - ii. Intravenous dosing guidelines

Table 12. Intravenous Phosphorus Dosing Guidelines

Serum Phosphorus (mg/dL)	General Medical-Surgical Population Dosage (mmol/kg) (Crit Care Med 1995;23:1504-11)	High Requirements^a Population (JPEN J Parenter Enteral Nutr 2006;30:209-14)
2.3–3	0.16	0.32
1.6–2.2	0.32	0.64
< 1.6	0.64	1

^aPatients with thermal injury (JPEN J Parenter Enteral Nutr 2001;25:152-9), those with trauma (especially those with a TBI) (JPEN J Parenter Enteral Nutr 2006;30:209-14; Nutrition 2010;26:784-90), those malnourished with evidence of significant complications from refeeding syndrome, or those with hepatic resections.

The drug should be mixed in 100–250 mL of normal saline or 5% dextrose in water and given at a rate no faster than 7.5 mmol/hour. Phosphorus should always be ordered in millimoles for ease of use and preparation. For ease of use and preparation in the pharmacy, phosphorus should be ordered in units divisible by 3 mmol (e.g., 15, 30, 45, 60) whenever possible.

Potassium phosphate salt can be used for patients with a serum potassium less than 4 (3 mmol P = 4.4 mEq potassium). Sodium phosphate salt should be used for patients with a serum potassium of 4 or greater (3 mmol P = 4 mEq Na).

- iii. Oral or enteral phosphorus dosing:
 - (a) Difficult to accomplish in patients not receiving EN because of single-entity products and doses needed for repletion and adverse GI effects (e.g., diarrhea)
 - (b) Neutra-Phos and Neutra-Phos K (only 8 mmol of phosphorus per tablet/packet)
 - (c) Can add potassium phosphate/sodium phosphate injection to enteral feeding solution (e.g., 30 mmol/L) or oral sodium phosphate solution 5–10 mL per liter of EN (5 mL = 20 mmol of phosphorus)
- 3. Hyperphosphatemia
 - a. Definition: Serum phosphorus concentration greater than 5 mg/dL, usually not clinically relevant until serum phosphorus is greater than 6 mg/dL
 - b. Signs and symptoms: Hypocalcemia and metastatic calcification (e.g., neuromuscular irritability, prolonged QT interval, tetany) – Usually does not occur until the serum calcium-phosphorus product approaches 55 or greater (Adv Exp Med Biol 1978;103:195-201).
 - c. Etiologies:
 - i. Renal failure
 - ii. Immobility
 - iii. Chronic critical illness–associated metabolic bone disease
 - iv. Excessive phosphorus intake
 - v. Vitamin D toxicity
 - vi. Tumor lysis syndrome
 - vii. Hypoparathyroidism

- d. Treatment:
 - i. Reduce phosphorus intake (omit from PN solution, plus or minus reduce lipid content of PN solution if a high-fat formulation [controversial as phosphorus in organic form: phospholipids and not inorganic such as sodium phosphate]; change to “low- or no-electrolyte” renal enteral formula).
 - ii. Phosphate binders (Am J Health Syst Pharm 2005;62:2355-61)

Table 13. Phosphate Binders

Drug	Available Strength	Phosphorus-Binding Capacity	Recommended Empiric Initial Dose
Calcium carbonate ^a	500, 750, 1000 mg per tablet	Calcium 43 mg/g	1 g QID
Calcium acetate ^a	667 mg per tablet	Calcium 106 mg/g	1334–2001 mg TID
Sevelamer ^b	800 mg per capsule or packet	Sevelamer 80 mg/g	800–1600 mg TID
Lanthanum	250, 500, 750, 1000 mg per tablet	Data not available	500 mg TID

^aDo not use if the patient is hypercalcemic.

^bCarbonate comes in a powder; easier for administering to tube-fed patients; less likely to worsen metabolic acidosis than gel capsule in patients with renal failure because gel capsule is in hydrochloric acid salt form.

QID = four times daily; TID = three times daily.

II. ACID-BASE DISORDERS

A. Normal Homeostasis

1. Normal values

Table 14. Normal Blood Gas Values

Variables	Arterial Blood	Mixed Venous Blood
pH	7.35–7.45	7.31–7.41
P _{CO} ₂	35–45	41–51
P _O ₂	80–100	35–40
HCO ₃	22–26	22–26
Base excess	-2 to +2	-2 to +2
O ₂ saturation	> 95%	70%–75%

HCO₃ = bicarbonate.

2. Interpreting ABGs

- a. Acidemia (pH less than 7.35) versus alkalemia (pH greater than 7.45)
- b. Acidemia and alkalemia refer to an abnormal pH being either low or high, respectively. Acidosis and alkalosis refer to the metabolic or respiratory processes that led to the abnormal pH. Although the terms *emia* and *osis* are similar, they are uniquely different.

Table 15. Adverse Effects of Severe Acidemia (pH 7.25 or less)

Impaired cardiac output	Increased metabolic demands
Peripheral ischemia (centralization of blood)	Insulin resistance
Increased pulmonary vascular resistance	Decreased ATP synthesis
Hypotension	Increased protein breakdown
Increased risk of arrhythmias	Hyperkalemia
Decreased catecholamine responsiveness	Diaphragmatic fatigue/dyspnea
Obtundation/coma	Hyperventilation

Table 16. Adverse Effects of Severe Alkalemia (pH of 7.55 or greater)

Arteriolar constriction	Hypokalemia
Hypotension	Hypophosphatemia
Increased risk of arrhythmias	Hypocalcemia/tetany
Decreased coronary blood flow/decreased angina threshold	Organic acid production
Seizures	Hypoventilation/hypercapnia/hypoxemia
Lethargy, delirium, stupor	

For simple acid-base disorders, identify pH, Pco_2 , and HCO_3^- in that order. Whichever side of 7.40 the pH is on, the respiratory or metabolic processes that coincide with that pH abnormality are the primary etiology. If the pH is less than 7.40, an elevated Pco_2 (respiratory acidosis) or a decreased HCO_3^- (metabolic acidosis) is the primary etiology. If the pH is greater than 7.40, a decreased Pco_2 (respiratory alkalosis) or an increased HCO_3^- (metabolic alkalosis) is the primary etiology. An easy introductory overview to acid-base disorders by Haber is provided in the references (West J Med 1991;155:146-51).

However, sometimes more than one primary abnormality is present, or the anticipated compensatory process (metabolic or respiratory) is inadequate and may be contributing to the acid-base disorder. As a result, various formulas have been developed to predict what may be considered adequate compensation. However, many of these mathematical equations have limitations in their clinical utility and accuracy (Crit Care Med 2007;35:1264-70; Am J Resp Crit Care Med. 2000;162:2246-51; J Trauma Acute Care Surg 2012;73:27-32; Clin J Am Soc Nephrol 2007;2:162-74; Arch Intern Med 1992;152:1625-9) and can be difficult to memorize (West J Med 1991;155:146-51).

In addition, the issue of mixed acid-base disorders is confounded by several factors that can lead to errors in the interpretation of acid-base disorders. This would include non-steady-state conditions as well as the inability for the patient to adequately compensate through the respiratory pathway because of mechanical ventilator restrictions. Some of the more common equations for assessing acid-base disorders are discussed later in this chapter.

3. Use of base excess
 - a. Reflects the amount of base needed in vitro to return the plasma pH to 7.40 at standard conditions (Pco_2 40 mm Hg, 37°C)
 - b. Base excess reflects the metabolic component to interpreting the ABG. Some have described its use as a means for almost freeing the clinician from memorizing the “acid-base” correction formulas (described as follows). Despite its simplicity, it has limitations (J Trauma Acute Care Surg 2012;73:27-32). Crystalloid resuscitation (leading to hyperchloremic acidosis), exogenous bicarbonate administration, ethanol ingestion, and acetate/bicarbonate buffer in hemodialysis or CRRT solutions can lead to erroneous base excess calculations and errors in interpretation (J Trauma Acute Care Surg 2012;73:27-32).
4. Compensatory response to acid-base disorders

Table 17. Anticipated compensation to acid-base disorders (Crit Care 2000;4:6-14)

Primary Disorder	Serum HCO_3^- (mEq/L)	Anticipated Pco_2 (mm Hg)
Metabolic acidosis	≤ 22	$(1.5 \times \text{HCO}_3^-) + 8 (\pm 2)$
Metabolic alkalosis	≥ 28	$(0.7 \times \text{HCO}_3^-) + 21$
Primary disorder	Pco_2 (mm Hg)	Anticipated serum HCO_3^- (mEq/L)
Respiratory acidosis (acute) ^a	> 45	$[(\text{Pco}_2 - 40)/10] + 24$
Respiratory acidosis (chronic) ^a	> 45	$[(\text{Pco}_2 - 40)/3] + 24$ Or HCO_3^- should increase by ~ 4 mEq/L per 10-mm Hg increase in $\text{Pco}_2 > 40$
Respiratory alkalosis (acute) ^a	< 35	$24 - [(40 - \text{Pco}_2)/5]$
Respiratory alkalosis (chronic) ^a	< 35	$24 - [(40 - \text{Pco}_2)/2]$ Or For each 10-mm Hg decrease in Pco_2 , HCO_3^- should decrease by ~ 5 mEq/L

^aCompensation is different for acute versus chronic respiratory disorders because it takes about 2 days for the kidneys to adapt to a persistent change in respiratory status.

B. Respiratory Acidosis

1. Make sure it is not caused by excessive sedation/analgesia or overfeeding with EN/PN.
2. Metabolic compensation – See Table 17.

C. Respiratory Alkalosis

1. Make sure the patient is getting adequate sedation/analgesia, fever/pneumonia is being treated; nicotine and drug withdrawal regimen is/are appropriate
2. Metabolic compensation – See Table 17

D. Metabolic Acidosis

1. Use of the serum anion gap (AG)
 - a. Used to determine the etiology for the metabolic acidosis. AG is the difference between major cations and anions in blood (trying to detect whether there is an abundance of unmeasured anions).

$$\text{AG} = (\text{Na} + \text{K}) - (\text{Cl} + \text{HCO}_3^-)$$
 - b. Normal range is around 3–12 mEq/L. Because serum potassium is small, it is not often used when calculating cations (e.g., Na^+)
 - c. Some clinicians adjust AG for serum albumin (Crit Care Med 1998;26:1807-10) and phosphorus (Crit Care Med 2007;35:2630-6) (serum albumin concentration should be multiplied by 2–2.3, and serum phosphorus [milligrams per deciliter] should be multiplied by 0.5, and both should be added to the anions [e.g., chloride plus bicarbonate]). Using this method, the adjusted AG (or sometimes called the strong ion gap when referring to the physicochemical methodology for interpreting acid-base disorders) should be close to 0 (± 2) if the patient does not have an AG acidosis.
 - d. Causes of an AG acidosis: One easy mnemonic to remember (there are others) is A MUD PIE:
 A = aspirin (or other salicylates)
 M = methanol
 U = uremia (including rhabdomyolysis)
 D = diabetes (diabetic ketoacidosis)

- P = paraldehyde
 I = infection or ischemia (lactic acidosis)
 E = ethylene glycol or ethanol toxicity
- e. Types of lactic acidosis (lactate greater than 18/dL and pH less than 7.35)
 - i. Type A: Hypoperfusion (cardiogenic or septic shock, regional ischemia, severe anemia)
 - ii. Type B: Metabolic – No tissue hypoxia
 - (a) B1 = sepsis without shock, liver disease, leukemia, lymphoma, AIDS (acquired immunodeficiency syndrome)
 - (b) B2 = drugs/toxins (metformin, didanosine/stavudine/zidovudine, ethanol, linezolid, propofol, propylene glycol toxicity caused by intravenous lorazepam or pentobarbital), nitroprusside (cyanide) toxicity
 - (c) B3 = inborn errors of metabolism (pyruvate dehydrogenase deficiency)
 - f. Causes of a normal AG acidosis
2. Another easy mnemonic to remember (there are others) is ACCRUED.

A = Ammonium chloride/acetazolamide (urine bicarbonate loss)
 C = Chloride intake (PN, intravenous solutions)
 C = Cholestyramine (GI bicarbonate loss)
 R = Renal tubular acidosis: Types I, II, and IV
 U = Urine diverted into the intestine (e.g., ileal conduit, vesicoenteric fistula)
 E = Endocrine disorders (e.g., aldosterone deficiency)
 D = Diarrhea or small/large bowel fluid losses (e.g., enterocutaneous fistulas)
 3. Use of the delta ratio for determining mixed acid-base disorders
 Delta ratio =

$$\Delta AG / \Delta HCO_3 = (\text{measured AG} - \text{normal AG}) / (\text{normal HCO}_3 - \text{measured HCO}_3) = (AG - 14) / (24 - \text{measured HCO}_3)$$

Table 18. Interpreting delta ratio

Delta Ratio	Assessment
< 0.4	Hyperchloremic normal AG acidosis
< 1	High AG acidosis and normal AG acidosis
1–2	AG acidosis
> 2	High AG acidosis and concurrent metabolic alkalosis OR a preexisting compensated respiratory alkalosis

4. An alternative method (and perhaps a simpler approach) to the delta ratio is to calculate the “excess gap” compared with the AG (West J Med 1991;155:146-51).
 Excess gap = AG – 12 (12 being the upper limit of normal for AG).
5. The excess gap is then added to the measured serum bicarbonate concentration. If the sum is less than a normal serum bicarbonate concentration (e.g., 28–30 mEq/L), a mixed AG and non-AG acidosis is present. If the sum is greater than a normal bicarbonate concentration, the patient likely has an AG acidosis and concurrent metabolic alkalosis.
6. Evaluation of respiratory compensation: See Table 17
7. Treatment
 - a. Aggressive interventional therapy unnecessary until pH less than 7.20–7.25
 - b. Treat primary etiology! This should be the focus of treating the acid-base disorder.

- c. Intravenous sources of alkali – Done conservatively in conjunction with treating primary disorder whenever possible. The intent is not to normalize the pH but to improve the pH (definitely avoid overcorrection).
 - i. Sodium bicarbonate – Most commonly used
 - ii. Sodium acetate – Available in PN solutions
 - iii. Sodium citrate – Used orally for patients with chronic kidney injury
 - iv. THAM (0.3 N tromethamine) – Possibly indicated for patients with chronic and severe hypercapnia or extreme volume overload (very rarely used in our clinical practice; however, some institutions have had to use THAM more often in recent years because of intravenous crystalloid/bicarbonate shortages)
- d. Total bicarbonate dose (mEq) = $0.5 \times \text{Wt (kg)} \times (24 - \text{HCO}_3)$
 - i. Give one-third to one-half of the calculated total dose (or 1–2 mEq/kg) over several hours to achieve a pH of around 7.25 (avoid boluses if possible).
 - ii. Once the pH is around 7.25 or greater, slower correction without increasing bicarbonate more than 4–6 mEq/L to avoid exceeding the target pH
 - iii. Serial ABGs (e.g., every 6 hours), watch rate of decrease in serum potassium
 - iv. Use of sodium bicarbonate injection is controversial in patients with lactic acidosis (Curr Opin Crit Care 2008;14:379-83).
- e. Adverse effects of sodium bicarbonate excess:
 - i. Hypernatremia, hyperosmolality, volume overload
 - ii. Hypokalemia, hypocalcemia, hypophosphatemia
 - iii. Paradoxical worsening of the acidosis (if the fractional increase in PCO_2 production exceeds the fractional bicarbonate change)
 - iv. Over-alkalinization
- f. THAM – Shorter duration of action than sodium bicarbonate and appears not to decrease serum potassium. (J Nephrol 2005;18:303-7)

Patient Case

Questions 8 and 9 pertain to the following case.

A 70-year-old woman (weight 50 kg) who underwent a radical cystectomy with ileal conduit urinary diversion for bladder cancer develops a postoperative ileus and requires PN. Her NG fluid output is about 1–1.5 L/day, and she has been receiving esomeprazole. Her current intravenous solutions include 0.45% sodium chloride with potassium chloride 20 mEq/L at 50 mL/hour in addition to her PN. Total daily electrolyte intake from the PN is as follows: sodium chloride 60 mEq/day, potassium acetate 40 mEq/day, sodium phosphate 15 mmol/day, magnesium 24 mEq/day, and calcium gluconate 10 mEq/day. After several days of PN therapy, she has the following serum electrolyte perturbations: sodium 141 mEq/L, potassium 3.9 mEq/L, chloride 117 mEq/L, total CO_2 content 22 mEq/L, BUN 14 mg/dL, and SCr 0.8 mg/dL. Her ABG revealed the following: pH 7.29, PO_2 95 mmHg, PCO_2 35 mm Hg, and bicarbonate 21 mEq/L.

8. Which best describes the patient's type of acid-base disorder?
- A. Hyperchloremic, normal AG acidosis.
 - B. AG acidosis.
 - C. AG acidosis with hyperchloremia.
 - D. Respiratory acidosis with concurrent metabolic alkalosis.

Patient Case (*continued*)

9. Which is the most appropriate treatment algorithm for this patient?

- A. Substitute the sodium chloride in the PN solution for sodium acetate.
- B. Sodium bicarbonate 100 mEq intravenously.
- C. Change the supplemental intravenous solution to Ringer lactate solution.
- D. Add 100 mEq of sodium bicarbonate to the PN solution.

E. Metabolic Alkalosis: pH greater than 7.45; symptoms are not usually severe until pH is greater than 7.55–7.60

1. Assessment (to help guide treatment) based on urinary chloride
 - a. Saline responsive (urinary chloride less than 10 mEq/L)
 - i. Excessive gastric fluid losses
 - ii. Diuretic therapy (especially loop diuretics)
 - iii. Dehydration (contraction alkalosis)
 - iv. Hypokalemia
 - v. (Over-) Correction of chronic hypercapnia
 - b. Saline resistant (urinary chloride greater than 20 mEq/L)
 - i. Excessive mineralocorticoid activity (e.g., hydrocortisone)
 - ii. Excessive alkali intake
 - iii. Profound potassium depletion (serum potassium less than 3 mEq/L)
 - iv. Excess licorice (mineralocorticoid) intake
 - v. Massive blood transfusion
 - c. Respiratory compensation (highly variable and may not be possible for ventilator-dependent patients)
 - d. Intravascular volume status (important for saline-responsive alkalemia)
2. Treatment – Saline-responsive alkalemia
 - a. Treat underlying cause (if possible).
 - b. Decreased intracellular volume? Give intravenous 0.9% sodium chloride infusion (with potassium chloride, if necessary).
 - c. Increased intracellular volume? Acetazolamide 250–500 mg orally or intravenously once to four times daily plus potassium chloride if necessary (Intensive Care Med 2010;36:859-63; Acta Anaesthesiol Scand 1983;27:252-4; Crit Care Med 1999;27:1257-61).
 - i. Hydrochloric acid therapy if alkalosis persistent or initial pH greater than 7.6
 - (a) N or 0.2 N of hydrochloric acid (use 0.2 N for patients requiring fluid restriction).
Hydrochloric acid should be given by central venous administration, and it requires delivery in a glass bottle.
 - ii. Dosage of hydrochloric acid:
 - (a) Chloride deficit (Arch Surg 1975;110:819-21):
Dose (mEq) = 0.2 L/kg x Wt (kg) x (103 – serum chloride)
 - (b) Bicarbonate excess (J Am Soc Nephrol 2000;11:369-75):
Dose (mEq) = 0.5 L/kg x Wt (kg) x (serum HCO₃⁻ - 24)
 - (c) Dickerson's empiric approach: Give one-half of calculated dose over 12 hours, repeat ABG at 6 and 12 hours after initiating hydrochloric acid infusion, and readjust infusion rate if necessary; continue therapy and monitoring until pH less than 7.5; then stop and reassess

3. Treatment – Saline-unresponsive alkalosis: Treat underlying cause (if possible).
 - a. Exogenous corticosteroids – Decrease dose or use drug with less mineralocorticoid effect.
 - b. Excessive alkali intake – Alter regimen.
 - c. Profound hypokalemia (serum potassium less than 3 mEq/L) – Aggressive potassium supplementation
 - d. Rare causes: Endogenous mineralocorticoid excess (Bartter or Gitelman syndrome) – Spironolactone, amiloride, or triamterene; consider surgery
 - e. Liddle syndrome: Amiloride or triamterene

- F. The Stewart or Physicochemical Approach to Acid-Base Disorders – This emerging approach to acid-base disorders is based on charge differences between ions. Essentially, acid-base disorders can be defined by differences between the activity of abundant cations (sodium, potassium, ionized calcium, ionized magnesium) and the activity of all abundant anions (chloride, lactate). The influence of albumin and serum phosphate is also considered. Although this technique has advantages over the traditional method discussed herein, the Stewart approach has been criticized by others because it offers no diagnostic or prognostic advantages over the traditional/bicarbonate analysis (Crit Care Med 2007;35:1264-70). The reader is referred elsewhere for additional information on this methodology (Crit Care Med 2004;32:1120-4; J Trauma 2009;66:1045-51; J Crit Care.1995;10:51-5).

III. NUTRITION SUPPORT

- A. Nutritional Assessment
 1. Classes of malnutrition
 - a. “New” American Society for Parenteral and Enteral Nutrition (ASPEN) international consensus nomenclature (JPEN J Parenter Enteral Nutr 2010;34:156-9)
 - i. Starvation-related malnutrition (e.g., anorexia nervosa)
 - ii. Chronic disease-related malnutrition (e.g., Crohn disease, organ failure)
 - iii. Acute disease or injury-related malnutrition (e.g., major infection, burns, trauma)
 - b. “Classic” definition
 - i. Marasmus (e.g., decreased fat/muscle protein stores but normal serum proteins)
 - ii. Kwashiorkor (e.g., normal fat, decreased muscle protein, decreased serum proteins)
 - iii. Kwashiorkor-Marasmus mix (decreased fat, muscle protein, and serum proteins)
 - c. Based on weight loss – A 10% unintentional weight loss within a 6-month period is considered significant.
 - d. Based on current weight
 - i. Mild malnutrition: 80%–89% ideal body weight (IBW)*
 - ii. Moderate malnutrition: 70%–79% IBW*
 - iii. Severe malnutrition: Less than 70% IBW*
 - iv. Obese: Greater than 130% IBW*

*IBW: Female = 45.5 kg/5 ft plus 2.3 kg per inch above 5 ft
 Male = 50 kg/5 ft plus 2.3 kg per inch above 5 ft
 - e. Based on body mass index (BMI) = weight (kg)/height² (m²)
 - i. Less than 18.5: Underweight
 - ii. 18.5–24.9: Normal
 - iii. 25–29.9: Overweight
 - iv. 30–34.9: Class I obesity
 - v. 35–39.9: Class II obesity
 - vi. Greater than 40: Class III obesity
 - f. Empiric weight adjustment for amputations

Table 19. Body compartments contribution to body weight (J Am Diet Assoc 1995;95:215-8)

Body Part Amputation	Approximate Contribution to Body Weight (%)
Foot	1.5
Calf, foot	5.9
Leg (from hip)	16
Hand	0.7
Hand and forearm	2.3
Arm	5

2. Serum proteins used in nutritional assessment

- a. Albumin: Half-life 20 days
 - i. Depletion: Mild 2.8–3.5 g/dL, moderate 2.1–2.7 g/dL, severe less than 2.1 g/dL
 - ii. Limitations: Long half-life, large body pool; is a negative acute-phase reactant protein that decreases in response to infection, inflammation, surgery, injury, or other acute event
- b. Transferrin: Half-life 7 days
 - i. Depletion: Mild 150–250 mg/dL, moderate 100–150 mg/dL, severe less than 100 mg/dL
 - ii. Limitations: Increased with iron deficiency; is a negative acute-phase reactant protein that decreases in response to infection inflammation, surgery, injury or other acute event
- c. Prealbumin: Half-life 2 days
 - i. Depletion: Mild 10–15 mg/dL, moderate 7–10 mg/dL, severe less than 7 mg/dL
 - ii. Limitations: Increased with CKD; is a negative acute-phase protein that decreases in response to infection, inflammation, surgery, injury, or other acute event
- d. Physical examination: Loss of subcutaneous body fat, muscle atrophy (including temporal wasting), presence of lower extremity edema and/or ascites
- e. Subjective Global Assessment (JPEN J Parenter Enteral Nutr 1987;11:8-13): Incorporates overall evaluation by incorporating five elements of the patient's history (presence of weight loss, dietary intake change, presence of significant adverse GI symptoms persistent for more than 2 weeks, physical functional capacity, and metabolic demands of the patient's disease state) and physical examination

B. Energy Requirements

1. Assessing caloric requirements: Indirect calorimetry – Measured energy expenditure by oxygen consumption and CO₂ production – The “gold standard”
 - a. Respiratory quotient (VCO₂/Vo₂); 1 for carbohydrate oxidation; 0.7 for fat oxidation; 0.8 for protein oxidation; greater than 1 usually implies overfeeding (net fat synthesis), less than 0.7 suggests ketosis or an error in measurement (too much fraction of inspired oxygen [Fio₂] variability at higher Fio₂ concentrations)
 - b. Organization guideline recommendations

Table 20. Guideline recommendations for caloric intake

Organization	Recommendation
American College of Chest Physicians (Chest 1997;111:769-78)	25 kcal/kg/day; increase by 10%–20% with SIRS
SCCM/ASPEN (JPEN J Parenter Enteral Nutr 2009;33:277-316)	25–30 kcal/kg/day or use of indirect calorimetry
ESPEN PN (Clin Nutr 2009;28:387-400)	25 kcal/kg/day (in the absence of measured REE)
ESPEN EN (Clin Nutr 2006;25:210-23)	20–25 kcal/kg/day (during acute phase) 25–30 kcal/kg/day (during recovery)
ASPEN Obesity (JPEN J Parenter Enteral Nutr 2013;37:714-44)	< 14 kcal/kg actual weight/day or 50%–70% of estimated requirements when given with a high protein intake
Eastern Association for Surgery of Trauma (J Trauma 2004;57:660-9)	25–30 kcal/kg/day or 1.2–1.4 x BEE (Harris-Benedict equations) or 1.2–1.4 x BEE (Harris-Benedict equations), 30 kcal/kg/day (1.4 x BEE) for patients with TBI, 22–25 kcal/kg/day for paraplegics, 20–22 kcal/kg for quadriplegics

BEE = basal energy expenditure; ESPEN = European Society for Clinical Nutrition and Metabolism; REE = resting energy expenditure; SCCM = Society of Critical Care Medicine.

c. Predictive methods

- i. Mifflin-St. Jeor equations (preferred for non-ventilator-dependent obese patients with AKI or CKD or hepatic encephalopathy when a hypocaloric, high-protein regimen is not possible)

(a) Females = $(10 \times \text{Wt}) + (6.25 \times \text{Ht}) - (5 \times \text{A}) - 161^*$

(b) Males = $(10 \times \text{Wt}) + (6.25 \times \text{Ht}) - (5 \times \text{A}) + 5^*$

*Age (years); Ht (centimeters); Wt = actual body weight (kilograms).

- ii. Penn State equation (preferred for ventilator-dependent obese patients with AKI or CKD or hepatic encephalopathy when a hypocaloric, high-protein regimen is not possible):

$\text{REE} = (\text{Mifflin} \times 0.96) + (\text{Tmax} \times 167) + (\text{Ve} \times 31) - 6212^*$

*REE = resting energy expenditure; Tmax = maximum temperature in degrees Celsius;

Ve = minute ventilation, L/min.

- iii. Modified Penn State equation (preferred for ventilator-dependent obese patients 60 years or older with AKI or CKD or hepatic encephalopathy when a hypocaloric, high-protein regimen is not possible)

$\text{REE} = (\text{Mifflin} \times 0.71) + (\text{Tmax} \times 85) + (\text{Ve} \times 64) - 3085^*$

*Tmax = maximum temperature in degrees Celsius; Ve = minute ventilation, L/min.

- iv. Basal energy expenditure (BEE) – Harris-Benedict equations (preferred for small adults and elderly patients)

(a) Females = $655 + (9.6 \times \text{Wt}) + (1.7 \times \text{Ht}) - (4.7 \times \text{A})^*$

(b) Males = $66 + (13.7 \times \text{Wt}) + (5 \times \text{Ht}) - (6.8 \times \text{A})^*$

*Wt (kilograms), Ht (centimeters), Age (years).

- d. Adverse effects of overfeeding – Do not exceed 5 mg/kg/minute of glucose/carbohydrate (Ann Surg 1979;190:274-85); limit total caloric intake (do not exceed 1.3–1.5 x measured resting energy expenditure); do not exceed intravenous fat intake of 2.5 g/kg/day (most clinicians limit intravenous fat to around 1.5 g/kg/day or less).

- i. **Hypercapnia:** It was traditionally thought that excessive glucose intake alone was responsible for hypercapnia observed during overfeeding. However, studies of acutely ill patients showed that aggressive feeding resulted in marked increases in CO₂ production (Ann Surg 1980;191:40-6; JAMA 1980;243:1444-7). Substitution of glucose kilocalories with lipid decreases CO₂ production (Anesthesiology 1981;54:373-7) when overfeeding but does not alter CO₂ production if not overfeeding (e.g., 1.3 x BEE) (Chest 1992;102:551-5). Because most institutions lack the ability to measure energy expenditure, estimates are used. If the patient experiences hypercapnia without a known cause, the nutrition therapy should be suspected and the caloric intake empirically decreased (especially if the patient is having trouble weaning from the ventilator).
- ii. **Hyperglycemia:** In a retrospective study of 102 PN-fed patients not predisposed to hyperglycemia, dextrose intakes in excess of 5 mg/kg/minute resulted in substantial hyperglycemia (blood glucose [BG] greater than 200 mg/dL) in 18 of 37 patients (Nutr Clin Pract 1996;11:151-6). Patients with stress-induced hyperglycemia or diabetes are even more susceptible to hyperglycemia with EN or PN.
- iii. **Fatty infiltration of the liver:** May be owing to overfeeding with fat or carbohydrate. Usually presents as a cholestatic liver disease (increased γ -glutamyltransferase, alkaline phosphatase, and ultimately bilirubin) after at least 1 week to 10 days of overfeeding (Arch Surg 1978;113:504-8). May be transient or reversible or can progress to end-stage liver disease. Over a few weeks, patients can appear jaundiced. Patients with critical illness and/or infections tend to be more susceptible to hepatic steatosis compared with non-critically ill patients (possibly because of an exaggerated inflammatory process). Although treatment with fish oil appears promising in infants and children (Ann Surg 2009;250:395-402; Nutr Clin Pract 2013;28:30-9), data for adults are lacking. Usual management for adult patients with suspected PN-associated liver disease is first to ensure the patient is not being overfed and given a mixed-fuel PN solution, followed by cyclic PN (PN is infused over part of the day). Reinstitution of EN as soon as possible (if possible) is of utmost importance.
- e. **Recommendations for caloric requirements***
 - i. Maintenance OR elective surgery: 25 kcal/kg/day
 - ii. Malnourished, nutritionally depleted: 1.4–1.5 x BEE
 - iii. Medical ICU patients: 25–30 kcal/kg/day
 - iv. Minor infection or surgery: 25–30 kcal/kg/day
 - v. Major surgery/trauma/sepsis: 30–32 kcal/kg/day
 - vi. Obese (hypocaloric) nutrition: 22–25 kcal/kg IBW/day or less
 - vii. Older (older than 65 years): 1.3–1.5 x BEE
 - viii. Smaller patients (weight 50 kg or less): 1.3–1.5 x BEE

*These are general recommendations, based on the lack of measured energy expenditure, from this author's practice, which are subject to exception depending on prevailing disease states, organ failures, extent of malnourishment, provision of paralytic drugs/pentobarbital/propofol, and types of injuries.

C. Protein Requirements

1. Guideline recommendations

Table 21. Guideline recommendations for protein intake

Organization	Recommendation
American College of Chest Physicians (Chest 1997;111:769-78)	1.2–1.5 g/kg/day; 1.5–2 g/kg/day not to exceed 2 g/kg/day with SIRS; routine NB determinations recommended
SCCM/ASPEN (JPEN J Parenter Enteral Nutr 2009;33:277-316)	1.2–2 g/kg/day; higher amounts are likely needed for multiple trauma or burns
ESPEN PN (Clin Nutr 2009;28:387-400)	1.3–1.5 g/kg IBW/day
ESPEN EN (Clin Nutr 2006;25:210-23)	Not given
ASPEN Obesity (JPEN J Parenter Enteral Nutr 2013;37:714-44)	1.2 g/kg actual weight/day or 2–2.5 g/kg IBW/day when given with a hypocaloric regimen
Eastern Association for Surgery of Trauma (J Trauma 2004;57:660-9)	1.25–2 g/kg/day; 2 g/kg/day for burns

2. Recommendations for protein requirements*

- a. Maintenance or elective surgery: 0.8–1 g/kg/day
- b. Minor infection or surgery: 1.2–1.5 g/kg/day
- c. Malnourished, nutritionally depleted: 1.5 g/kg/day
- d. Medical ICU patients: 1.5–2 g/kg/day
- e. Major surgery/trauma/sepsis: 2–2.5 g/kg/day
- f. Renal failure
 - i. AKI: 0.6–1 g/kg/day
 - ii. CKD: 0.6–1 g/kg/day
 - iii. Hemodialysis: 1–1.5 g/kg/day
 - iv. CRRT: 2–2.5 g/kg/day
- g. Obese, hypocaloric
 - i. BMI less than 40: 2 g/kg IBW/day
 - ii. BMI of 40 or greater: 2.5 g/kg IBW/day

*Ideally, this intake should be adjusted according to the results of an NB determination, when possible.

Patient Case

10. A 40-kg woman admitted to the trauma ICU receives a PN solution containing 350 g of dextrose, 160 g of amino acids, and 80 g of lipid daily. She has normal renal and hepatic function. Her most recent ABG from the morning shows a pH of 7.30, P_{CO_2} of 55 mm Hg, P_{O_2} of 96 mm Hg, and bicarbonate of 31. Her fingerstick BG values from the past 24 hours range from 150 to 180 mg/dL. Which would be best to recommend concerning her PN?
 - A. Decrease dextrose to 175 g/day, and increase lipid to 120 g/day.
 - B. Add 20 units of regular human insulin per day to the PN solution.
 - C. Decrease all the macronutrients by about one-half.
 - D. Increase the acetate content of the PN solution.

3. Assessing protein requirements: NB
 - a. $NB = \text{nitrogen in } (N_{in}) - \text{nitrogen out } (N_{out})$
 - b. To calculate N_{in} :
 - i. Add all daily protein intake sources together, including the protein in EN, liquid protein supplements, oral dietary supplements, and/or PN solution.
 - ii. Convert protein intake (grams per day) to nitrogen intake (grams per day):
 $N_{in} \text{ (g/day)} = \text{protein (g/day)} / 6.25$ (assumes good-quality protein as 16% nitrogen content)
 - iii. To calculate N_{out} : $N_{out} \text{ (g/day)} = (UUN + 4 \text{ g})^* + \text{BUN change correction (if necessary)}$, where UUN is 24-hour urine urea nitrogen excretion (grams per day).
 - iv. *For patients with high UUN excretion (e.g., greater than 15 g/day), $UUN / 0.85 + 2$ may be a more reliable estimate of total urinary nitrogen excretion loss and stool/integumentary losses (Nutrition 2005;21:332-8).

BUN Change Estimation

$\text{BUN adjustment (g/day)} = [\text{change in BUN (mg/dL)} \times 0.01] \times [\text{body water (L/kg)} \times \text{Wt (kg)}]$

Use only if BUN change is 5 mg/dL or greater.

Body water = 0.6 L/kg for males; 0.55 L/kg for females

- v. Calculate the NB: $NB \text{ (g/day)} = N_{in} \text{ g/day} - N_{out} \text{ g/day}$.
 - vi. Measured versus predicted creatinine clearance (for gross assessment of adequacy in the 24-hour urine collection)
 - vii. Serum prealbumin changes are unreliable because of the influence of stress/inflammation; some clinicians will obtain a serum C-reactive protein concentration together with a serum prealbumin concentration for assessment.
4. Does more protein really make a difference?
 - a. Weijs (2012) (JPEN J Parenter Enteral Nutr 2012;36:60-8): 28-day mortality improved in those who received an average of 1.3 g/kg/day versus 1.1 or 0.8 g/kg/day (886 mixed ICU patients).
 - b. Allingstrup (2012) (Clin Nutr 2012;31:462-8): 28-day mortality improved in those who received an average of 1.5 g/kg/day versus 1.1 or 0.8 g/kg/day (113 mixed ICU patients).

Patient Case

Questions 11–13 pertain to the following case.

A 45-year-old man with obesity (BMI 35 kg/m², IBW 75 kg; current body weight 114 kg), acute pancreatitis, and sepsis was given a PN solution containing 200 g of dextrose, 150 g of amino acids, and 50 g of 20% lipids daily.

11. Which best depicts the kilocalories and protein this regimen will provide (normalized to IBW)?
 - A. 24 kcal/kg IBW/day and 2 g/kg IBW/day.
 - B. 27 kcal/kg IBW/day and 2 g/kg IBW/day.
 - C. 16 kcal/kg IBW/day and 1.3 g/kg IBW/day.
 - D. 20 kcal/kg IBW/day and 1.3 g/kg IBW/day.

Patient Case (*continued*)

A 24-hour urine collection was done to determine the NB. The UUN concentration was 900 mg/dL, and the urine volume output was 3000 mL. The patient's BUN was essentially unchanged during the NB determination.

12. Using the "classic nitrogen balance equation" ($NB = N_{in} - UUN - 4$), which most accurately depicts the patient's NB?
 - A. +4 g/day.
 - B. -4 g/day.
 - C. -7 g/day.
 - D. -10 g/day.
13. Which changes would be best to make to the patient's PN regimen?
 - A. Increase the protein and non-protein energy content.
 - B. Increase the protein content, and decrease the non-protein energy content.
 - C. Increase the protein content.
 - D. Increase the non-protein energy content.

D. Principles of EN and PN

1. Indications for EN: If the patient is unable to eat adequate amounts to achieve goal nutritional intakes. EN is preferred to PN because EN has less infectious complications (Ann Surg 1992;215:503-13; JPEN J Parenter Enteral Nutr 2009;33:277-316). This position is universally accepted among all guideline sources.
 - a. Lack of bowel sounds, flatus, or bowel movement is not a contraindication for EN because these are non-specific indicators of GI function (SCCM/ASPEN 2009; (JPEN J Parenter Enteral Nutr 2009;33:277-316).
 - b. Evidence of ileus (e.g., dilated loops of bowel on abdominal radiography) is, however, a contraindication for EN.
 - c. High NG output (greater than around 800 mL NG output) in a 24-hour period might indicate delayed gastric emptying, and the patient might not be ready for EN when fed into the stomach and post-pyloric feeding is not possible. If the patient's GI function appears to be improving, clamp NG tube for 4 hours and check GRV (if GRV is less than around 250 mL and the abdomen is not distended, patient is probably ready for gastric feeding). Note: This is our Nutrition Support Service's empiric practice and cannot be found in any guideline recommendations. See section G2, "GRVs and prokinetic agents," that follows for an expanded discussion on when/how to use prokinetic pharmacotherapy for patients with gastric feeding intolerance.
 - d. Refusal to eat/anorexia is not an absolute contraindication for EN. Ensure appropriate dietary preferences, and add high-calorie/protein liquid supplements to meals and bedtime snack first.
2. EN formulas

Table 22. EN Formulas

Product Category	Indication	Macronutrients	Additional Comments	Examples
Standard tube feeding	Minimal stress	1–1.2 kcal/mL Protein 40–50 g/L	Polymeric, 300–500 mOsm/kg, fiber	Jevity, Nutren 1.0, Fibersource HN
Volume restricted	Congestive heart failure, fluid-restricted patients	2 kcal/mL Protein 60–80 g/L	Polymeric, 700–800 mOsm/kg, fiber	Nutren 2.0, Resource 2.0, TwoCal HN
Renal	AKI (predialysis), renal dysfunction with increased serum potassium, Phos, Mg	2 kcal/mL Protein 30–40 g/L	High calorie, low protein, no or low electrolytes, 600 mOsm/kg, volume restricted, fiber	Renalcal, Suplena
Renal	Renal failure with hemodialysis	2 kcal/mL Protein 80–90 g/L	High calorie, modest electrolytes, volume-restricted, 1000 mOsm/kg, fiber	Novasource Renal, Nepro
Increased protein needs	Critically ill patients (especially trauma, surgical, burns)	1 kcal/mL Protein 62 g/L	High-protein content, fiber, isotonic	Replete, Promote
Glucose intolerance	Hyperglycemia, diabetes mellitus	1.2 kcal/mL Protein 60 g/L	Low-carbohydrate content, fiber	Diabetisource AC, Glucerna 1.2
Immune enhancing	Critically ill surgical and trauma patients, perioperative GI cancer	1.5 kcal/mL Protein 90–94 g/L	Additional arginine, glutamine; fish oil	Impact Peptide 1.5, Pivot
Bariatric	Obese patients with good renal function	1 kcal/mL Protein 93 g/L	High protein, low calories	Peptamen Bariatric
Elemental diet	Malabsorption, fat intolerance	1–1.5 kcal/mL Protein 50–68 g/L	Low fat/MCT, di/tripeptides/free AA, no fiber, low residue	Vivonex RTF Vital
Pulmonary	ARDS, ALI	1.2–1.5 kcal/mL Protein 63–76 g/L	Volume restricted, fish oil, low omega-6 fats	Oxepa Peptamen AF
Hepatic	Cirrhosis with hepatic encephalopathy	1.2–1.5 kcal/mL Protein 40–44 g/L	High branched chain, low aromatic AA	NutriHep Hepatic-Aid II
Protein supplement	High protein needs		Protein	Liquid or powder

AA = amino acids; ALS = acute lung injury; ARDS = acute respiratory distress syndrome; MCT = medium-chain triglyceride.

3. Tube feeding (TF) – Medication interactions: Hold TF 1 hour before and after drug administration (Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York: McGraw-Hill, 2011:2493-503).
*Increase TF rate to account for time off TF.
 - a. Warfarin (Pharmacotherapy 2008;28:308-13)
 - b. Phenytoin (Nutr Clin Pract 1996;11:28-31)
 - c. Levothyroxine (Nutr Clin Pract 2010;25:646-52; J Endocrinol Invest 2014;37:583-7)
 - d. Itraconazole (Antimicrob Agents Chemother 1997;41:2714-8)
 - e. Fluoroquinolones (J Antimicrob Chemother 1996;38:871-6)?
*Some clinicians have empirically increased the dosage of these drugs while giving continuous enteral feeding rather than holding the EN for 1 hour before and after drug administration. This author discourages this practice, especially for warfarin and phenytoin, because the doses necessary to overcome the effects of drug binding to the continuous EN are potentially toxic when the EN is held or discontinued without a dose adjustment. We have had limited success with preventing the development of subclinical or overt hypothyroidism by increasing the levothyroxine dose by 25 mcg/day temporarily while the patient is receiving continuous EN (Nutr Clin Pract 2010;25:646-52). Others have increased the ciprofloxacin dose to 750 mg twice daily during continuous EN to achieve therapeutic plasma concentrations well above the MIC (minimum inhibitory concentration) for a gram-negative urinary tract infection (J Antimicrob Chemother 1996;38:871-6).
4. Indications for PN
 - a. European Society for Clinical Nutrition and Metabolism (ESPEN) PN guidelines (2009) (Clin Nutr 2009;28:387-400): Patients who are not expected to receive EN within 3 days should receive PN within 24–48 hours if EN is contraindicated or if they cannot tolerate EN.
 - b. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): PN indicated only after the first 7 days of hospitalization when EN is not feasible or available.
 - c. Dickerson’s interpretation: The approach depends on several factors (e.g., if the patient is malnourished or wellnourished before ICU admission, patient population). Early nutrition (defined as within 24–72 hours according to published studies) appears to be beneficial for those with prolonged ICU stays and a high level of catabolism, including trauma, TBI, thermal injury, and some surgical subpopulations. Impact of early nutrition appears more variable with respect to clinical outcome for medical ICU patients and is likely related to a shorter duration in ICU stay and a lower level of catabolism for many patients.
5. PN formulations
 - a. Peripheral versus central venous administration
 - i. Osmolality of peripheral administration is limited to about 800 mOsm/kg.
 - ii. Because of the osmolality issue, peripheral PN solutions are “diluted,” requiring large volumes (contraindicated for fluid-restricted patients and difficult for older patients).
 - iii. Estimating the osmolality of PN solutions:
Approximate osmolality = [glucose g/L x 5] + [AA% x 100] + [lipid % x 15] + 200*
*Accounts for electrolytes/vitamins and can be variable, depending on amounts provided.
AA = amino acids.
 - iv. Phlebitis common with peripheral PN and difficult to use beyond 2–3 days
 - b. Safe practice guidelines for prescribing PN solutions – Should be prescribed in total amount per day (e.g., glucose 200 g/day, amino acids 150 g/day, lipid 30 g/day, fluid volume 2500 mL/day, sodium chloride 60 mEq/day, potassium acetate 80 mEq/day), NOT by concentrations (e.g., 20% dextrose in water, 8% amino acids) or by compounding techniques (e.g., 500 mL of 50% dextrose in water plus 500 mL of 10% amino acids).

- c. Glucose requirements
 - i. Obligatory requirements for central nervous system, renal medulla, bone marrow, leukocytes, etc.: Around 130 g/day
 - ii. Surgical wound about 80–150 g/day (based on atrioventricular differences and blood flow from a burned limb)
 - iii. Caloric contribution of glucose: 3.4 kcal/g (as opposed to carbohydrate 4 kcal/g)
 - iv. Mean glucose oxidation rate in critically ill patients is around 5 mg/kg/day (or about 25 kcal/kg/day as glucose). In general, most clinicians avoid exceeding this glucose intake.
- d. Lipid requirements
 - i. Main source is soybean oil – May be given separately from the PN admixture or as part of the PN solution. When given separately from the dextrose/amino acid formulation, the maximum allowable hang time according to the U.S. Food and Drug Administration (FDA) is 12 hours. With recent lipid shortages, olive oil–based intravenous lipid (which provides a more favorable cardiovascular lipid profile in patients on long-term PN) is now available from Canada. Intravenous fish oil requires permission from the FDA.
 - ii. Caloric contribution of intravenous fat emulsion: 10% = 1.1 kcal/mL; 20% = 2 kcal/mL; 30% = 3 kcal/mL or around 11 kcal/g for 10% emulsion, 10 kcal/g for 20% and 30% emulsion
 - iii. Dosage: About 100–150 g weekly (or 1–1.5 g/kg weekly) is enough to prevent essential fatty acid deficiency (EFAD). The FDA states a maximum upper limit of 2.5 g/kg/day in adults, though most clinicians try to keep the daily dose to 1.5 g/kg/day or less (see discussion on lipid emulsion and immune function in Controversial Topics section).
 - iv. Biochemical evidence for EFAD (the “classic definition” is an increased triene/tetraene [icosatrienoic acid/arachidonic acid] ratio greater than 0.4) occurs in 30%, 66%, 83%, and 100% of patients after 1, 2, 3, and 4 weeks of fat-free “full-calorie, continuous” PN (Surgery 1978;84:271-7). Clinical signs and symptoms of EFAD usually do not occur until about 2 weeks after biochemical evidence in adults. Since the investigators initiated intravenous lipid emulsion soon after the biochemical appearance of EFAD, only 2 of 32 patients developed clinical evidence suggestive of EFAD. EFAD can occur much sooner for infants and children. Obese patients receiving hypocaloric high-protein therapy can maintain normal plasma fatty acid profiles for up to 5 weeks (J Nutr Biochem 1994;5:243-7). Cyclic PN has been suggested to mobilize lipid from endogenous depots, but conclusive data are lacking.
 - v. Clinical symptoms (dry, scaly skin; hair loss; poor wound healing) occur about 2 weeks after biochemical evidence of deficiency in adults. Therefore, in most adults, the earliest you will see EFAD is after about 3 weeks of fat-free full-calorie continuous PN.
 - vi. Serum triglyceride concentration should be monitored at least weekly and more often for those with proven or suspected impaired triglyceride clearance.
 - vii. Predisposing conditions that may result in impaired clearance of triglycerides:
 - (a) Excessive lipid intake (often caused by propofol therapy)
 - (b) Acute pancreatitis
 - (c) Uncontrolled diabetes
 - (d) Liver failure
 - (e) Kidney failure (decreased lipoprotein lipase activity, carnitine deficiency with long-term hemodialysis patients)
 - (f) End-stage sepsis (multisystem organ failure)
 - (g) History of hyperlipidemia
 - (h) Obesity
 - (i) HIV (human immunodeficiency virus) (occurred even before current antiretroviral therapy) (Am J Med 1989;86:27-31)

- (j) Pregnancy
- (k) Small-for-gestational-age neonates (carnitine synthesis is maturational-dependent)
- viii. Propofol – A hidden source of lipids (10% soybean emulsion containing 1.1 kcal/mL)
- e. Electrolyte requirements (see Fluid and Electrolytes section)
- f. Vitamins (multivitamin infusion or multivitamin complex 10 mL/day; extra vitamins if patient has any vitamin deficiencies)
- g. Trace minerals (MTE-5 cocktail for normal requirements)
 - i. Zinc 3 mg/day normal requirements; 5 mg/day during critical illness; increased requirements for patients with diarrhea, intestinal fistulae. An additional 10 mg/day for a total of 13 mg/day is usually sufficient to meet increased intestinal losses (Gastroenterology 1979;76:458-67). Deficiency is characterized by loss of hair; erythematous rash, especially in periorbital regions of face; poor wound healing. Classic zinc deficiency is termed *acrodermatitis enteropathica*.
 - ii. Copper 0.3–0.5 mg/day is usually sufficient (Gastroenterology 1981;81:290-7). Copper deficiency is rare but is becoming more apparent in obese patients after gastric bypass procedures. Classic presentation of copper deficiency includes a “microcytic anemia unresponsive to iron therapy” or pancytopenia.
 - iii. Chromium 10–12 mcg/day normal requirements, up to 20 mcg/day for diarrhea. Rare. Classic presentation for deficiency is hyperglycemia.
 - iv. Manganese 150–300 mcg/day is probably enough. Some studies state that the amount of manganese contamination in the compounding of PN may be adequate as opposed to supplementation. Deficiency is very rare. Deficiency has been reported to present as a “diaper rash.” Several case reports of manganese toxicity associated with liver disease and high manganese intake (800 mcg – 1 mg/day) (Nutrition 2001;17:689-93). Signs and symptoms of toxicity emulate those of Parkinson disease.
 - v. Selenium 60 mcg/day up to 120 mcg/day for patients with diarrhea or short bowel syndrome. Deficiency results in extreme muscle weakness and congestive cardiomyopathy. Classic presentation with cardiomyopathy has been termed *Keshan disease* (named after a province in China where the first cases of selenium deficiency with cardiomyopathy were discovered).
 - vi. It is common clinical practice to withhold copper and manganese in the PN formulation for patients with hepatobiliary/cholestatic liver disease or a direct (conjugated) bilirubin concentration greater than 2 mg/dL.
 - vii. Some clinicians will withhold selenium for patients with significant renal disease who do not receive hemodialysis or CRRT, though the data in support of this practice are lacking.
- 6. Should supplemental PN be given to patients intolerant of EN?
 - a. ESPEN PN (2009) (Clin Nutr 2009;28:387-400): All patients receiving less than their target EN after 2 days should be considered for supplemental PN.
 - b. ESPEN EN (2006) (Clin Nutr 2006;25:210-23): For patients intolerant of EN, supplemental PN should be considered. Overfeeding should be avoided.
 - c. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): If patient is unable to meet energy requirements after 7–10 days of EN alone, consider initiating supplemental PN.
 - d. Canadian Practice Guidelines Update (2014) (Nutr Clin Pract 2014;29:29-43): It is strongly recommended that early supplemental PN or large volumes of hypertonic dextrose solutions not be used in unselected critically ill patients (i.e., low-risk patients with short stay in ICU). In the patient who is not tolerating adequate EN, data are insufficient to put forward a recommendation about when PN should be initiated.

- e. Caesar/EPaNIC study (N Engl J Med 2011;365:1-17) – 4640 mostly surgical patients, randomized controlled trial (RCT): EN only x 7 days; then PN initiated (hypertonic dextrose solutions x 2 days; then PN) versus supplemental PN in addition to whatever EN patients can tolerate during the first 7 days
 - i. Worsened survival (72% vs. 75%), greater infections (26% vs. 23%), ICU length of stay (LOS) greater than 3 days (51% vs. 48%) with early supplemental PN
 - ii. The patient population was limited in that malnourished (BMI less than 17 kg/m²) patients were excluded. Additionally, about 60% of the population were cardiac surgery patients which the indication for PN is questionable, 50% of patients were extubated by ICU day 2, and 70% of patients had an ICU LOS of only 3–4 days (which would imply a questionable severity of critical illness). Finally, only 58% of patients in the early PN group were even given PN (for 1 to 2 days) and only 25% patients in the late PN group ever received PN.
 - f. Heidegger (2013) (Lancet 2013;381:385-93): 307 patients, two medical centers, RCT: Patients who received less than 60% target from EN by day 3 with an anticipated ICU stay greater than 5 days received supplemental PN or EN alone. Supplemental PN was discontinued by day 8.
 - i. Supplemental PN group had decreased infections (27% vs. 38%).
 - ii. Smaller study compared with Caesar study. Not all patients had resting energy expenditure measured (some were predicted resting energy expenditure). Protein target was only 1.2 g/kg/day. No difference in ICU/hospital LOS, mortality
 - g. Dickerson's interpretation: Many of the patients in the Caesar study did not require PN to start with. PN should not be given indiscriminately to patients because of increased infectious complications in those who were not malnourished versus improved morbidity in perioperative malnourished patients with GI cancer (VA Cooperative Trial, 1991). Heidegger's data showed a benefit from supplemental PN in a sicker patient population than that in the Caesar study. Short-term supplemental PN may be indicated for patients anticipated to have prolonged duration of inability to use GI tract, anticipated prolonged duration of ICU stay, malnourished, and high level of catabolism, but the routine use of supplemental PN, for all patients, is discouraged. Effective use of prokinetic pharmacotherapy may also reduce the need for supplemental PN.
- E. Timing of Initiation of Nutrition Support: Early or not for ICU patients?
1. ESPEN EN (2006) (Clin Nutr 2006;25:210-23): Questionable benefit of early versus delayed EN; however, it was recommended that critically ill patients, who are hemodynamically stable and have a functioning GI tract, be fed early (less than 24 hours), if possible
 2. ESPEN PN (2009) (Clin Nutr 2009;28:387-400): All patients not expected to be on EN within 3 days should receive PN within 24–48 hours if EN is contraindicated or not tolerated.
 3. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): Early EN should be initiated within 24–48 hours after admission.
 4. Surviving Sepsis Campaign guidelines (2013) (Crit Care Med 2013;41:580-637): Administer oral nutrition or EN within the first 48 hours after severe sepsis is diagnosed.
 5. Dickerson's interpretation: The data are confusing because several studies and a meta-analysis in the literature have used different times for the definition of early nutrition therapy: 24, 36, 48, and 72 hours. Most evidence-based clinicians would suggest that nutrition therapy be initiated for most patients within 48 hours of ICU admission and definitely no later than 72 hours. Surgical ICU patients, including those with trauma and thermal injury, have been more consistently shown to benefit from early EN as opposed to more variable results for medical ICU patients.

F. Glycemic Control

1. Definition of the appropriate BG target range
 - a. Society of Critical Care Medicine (SCCM) guidelines (2012) (Crit Care Med 2012;40:3251-76): A BG of 150 mg/dL or greater should trigger initiation of insulin therapy to keep BG less than 150 mg/dL for most patients and maintain BG absolutely less than 180 mg/dL.
 - b. ASPEN guidelines (2013) (JPEN J Parenter Enteral Nutr 2013;37:23-36): A target BG range of 140–180 mg/dL is recommended.
 - c. Surviving Sepsis Campaign guidelines (2013) (Crit Care Med 2013;41:580-637): An insulin dosing protocol to keep BG less than 180 mg/dL, rather than an upper target of 110 mg/dL, is recommended when the patient has two consecutive BG measurements greater than 180 mg/dL.
 - d. American Diabetes Association (2014) (Diabetes Care 2014;37(suppl 1):S14-80): An insulin infusion should be used to control hyperglycemia, starting with a threshold no higher than 180 mg/dL. BG should be maintained between 140 and 180 mg/dL. Although strong evidence is lacking, lower glucose targets may be appropriate in select patients. BG targets less than 110 mg/dL are not recommended.
 - e. Dickerson's interpretation: Many evidence-based clinicians use a target BG range of 140–180 mg/dL when caring for patients in a mixed medical-surgical ICU. A growing amount of evidence from smaller studies shows that certain subpopulations such as trauma, traumatic brain injury, cardiothoracic surgery, and thermal injury may benefit from tighter BG (e.g., less than 140–150 mg/dL) control if it can be done safely without hypoglycemia.
2. BG monitoring frequency
 - a. SCCM guidelines (2012) (Crit Care Med 2012;40:3251-76): BG should be monitored every 1–2 hours for most patients receiving an insulin infusion; monitoring every 4 hours is not recommended because of the risk of unrecognized hypoglycemia.
 - b. Surviving Sepsis Campaign guidelines (2013) (Crit Care Med 2013;41:580-637): BG should be monitored every 1–2 hours during the insulin infusion and then extended to every 4 hours thereafter once stability in BG control achieved
 - c. American Diabetes Association (2014) (Diabetes Care 2014;37(suppl 1):S14-80): BG should be monitored every ½–2 hours during the insulin infusion.
 - d. Dickerson's interpretation: We monitor BG every hour and then extend it to every 2 hours once there is stability in BG control and the intravenous insulin infusion rate is demonstrated. Although some of the major trials show that BG monitoring could be extended to every 4 hours once two consecutive BG concentrations in the target range are achieved, we believe our patients are too labile to safely extend monitoring to every 4 hours. If they are stable enough to warrant BG monitoring every 4 hours, we will then begin to transition the EN-fed patient to intermediate- or long-acting subcutaneous insulin therapy (JPEN J Parenter Enteral Nutr 2013;37:506-16).
3. Point-of-care BG monitoring
 - a. SCCM guidelines (2012) (Crit Care Med 2012;40:3251-76): Point-of-care glucose meters are acceptable but not optimal for routine BG testing during an insulin infusion. Arterial or venous blood sampling, instead of fingerstick capillary BG testing, is suggested for patients in shock, on vasopressor therapy, or with severe peripheral edema.
 - b. At BG concentrations greater than 80 mg/dL, there was strong agreement (73% and 85%) in glycemic interventions when using either capillary or arterial BG measurements in critically ill patients (Intensive Care Med 2004;30:804-10).

- c. High doses of drugs such as acetaminophen, ascorbic acid, dopamine, or mannitol may interfere with the accuracy of BG measurements, and false elevation of results by point-of-care glucose meters that use the glucose-oxidase method may occur (Jacobi et al., 2012). Glucose-dehydrogenase-based assays are sensitive to interference and false elevation of results if the patient receives medications containing maltose (immunoglobulins) or icodextrin (used in some dialysis solutions).
 - d. Dickerson's interpretation: Point-of-care meters with capillary BG testing are probably acceptable for most critically ill patients as long as the patient's BG concentrations are not often less than 80 mg/dL. For low BG concentrations, point-of-care meters may erroneously report higher BG concentrations than measured (Crit Care Med 2009;37:2691-6). Patients with significant peripheral edema may also have erroneous BG concentrations.
4. Hypoglycemia
 - a. Most guidelines define hypoglycemia as a BG less than 70 mg/dL because increased glucagon, catecholamine, and growth hormone production occurs when the BG falls below this concentration. Mild to moderate hypoglycemia is usually defined as a BG concentration of 40–60 mg/dL (because autonomic symptoms usually appear) and severe (life threatening) hypoglycemia as less than 40 mg/dL.
 - b. Most common risk factors for hypoglycemia during insulin (Crit Care Med 2007;35:2262-7; Crit Care Med 2006;34:96-101)
 - i. Excessive insulin dose
 - ii. Abrupt discontinuation of EN or PN without an adjustment in the insulin therapy (purported to cause 62% of severe hypoglycemic events in the 2006 van den Berghe trial of medical ICU patients) (Crit Care Med 2012;40:3251-76)
 - iii. Renal failure (half-life of insulin is prolonged, ? impaired renal gluconeogenesis in response to hypoglycemia)
 - iv. Advanced age
 - v. Inotropes, vasopressor agents, octreotide with insulin therapy
 - vi. Sepsis
5. Transitioning from a continuous intravenous insulin infusion
 - a. Lack of a transition plan has been shown to result in loss of glycemic control. Different methods have been described in the literature, and the best approach depends on whether the patient is transitioning to an oral diet, bolus EN, or continuous EN (Crit Care Med 2012;40:3251-76; Diabetes Care 2014;37(suppl 1):S14-80; JPEN J Parenter Enteral Nutr 2013;37:506-16; The ASPEN Adult Nutrition Support Core Curriculum, 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition, 2012:580-602):
 - b. Example for transitioning from a continuous intravenous regular human insulin infusion to a subcutaneous intermediate acting insulin (neutral protamine Hagedorn [NPH]) for patients who receive continuous enteral feeding (JPEN J Parenter Enteral Nutr 2013;37:506-16)*
 - i. Give 30%–50% of the daily required intravenous regular human insulin, divided into two separate doses and given every 12 hours. Continue the graduated intravenous insulin infusion according to the algorithm.
 - ii. BG measurements are continued every 1–2 hours and are mapped to the timing of the subcutaneous NPH therapy to ascertain its pharmacokinetic peak and duration.
 - iii. The NPH dosage and interval are adjusted accordingly daily until the intravenous regular human insulin infusion is “auto-weaned” to about 1–2 units/hour.

- iv. The regular human insulin infusion is then discontinued with BG determinations, with sliding-scale regular human insulin coverage every 3–4 hours. The NPH is further titrated daily according to the required amount of corrective regular human insulin required to maintain BG within the target BG range.
- v. Frequency of BG measurements is decreased because the patient has stability in glycemic control.

*This method was evaluated in 32 patients who transitioned from a continuous intravenous regular human insulin to subcutaneous NPH and intermittent sliding-scale regular human insulin coverage (JPEN J Parenter Enteral Nutr 2013;37:506-16). BG concentrations were maintained in the target range for 18±3 hours/day. Eighteen patients (56%) experienced at least a single episode of moderate hypoglycemia (40–59 mg/dL), and three patients (9%) had an episode of severe hypoglycemia (BG less than 40 mg/dL). The overall rates of moderate and severe hypoglycemia were 1.3% and 0.1% of all BG determinations. Patients older than 60 years were at a higher risk of hypoglycemia than were younger patients.

Patient Case

14. A 55-year-old woman (75 kg) without diabetes is given PN after a major GI resection. She has been weaned from mechanical ventilation and is being transferred from the ICU to the floor. Her current PN formulation is 200 g of dextrose (1.8 mg/kg/minute), 110 g of amino acids, and 80 g of lipids (1.1 g/kg/day), which meets her goal requirements of protein at 26 kcal/kg/day and 1.5 g/kg/day. It contains regular human insulin at 20 units/day. During the past 24 hours, her fingerstick BG measurements have been between 170 and 210 mg/dL, and her serum glucose concentration is 182 mg/dL. She has received 14 units of sliding-scale regular human insulin coverage. Which would be best to suggest for optimal glycemic control?
 - A. Increase regular insulin to 30 units/day.
 - B. Decrease dextrose to 100 g/day.
 - C. Increase regular insulin to 50 units/day.
 - D. Do not change the current regimen.

G. Specialized and/or Controversial Topics in Nutrition Support Therapy for Critically Ill Patients

1. Trophic versus full EN—OR how much is enough to achieve a therapeutic benefit?
 - a. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): Efforts to provide greater than 50%–65% of goal calories should be made to achieve the clinical benefit of EN during the first week of hospitalization.
 - b. Surviving Sepsis Campaign guidelines (2013) (Crit Care Med 2013;41:580-637): Avoid mandatory full-caloric feeding in the first week; instead, suggest low-dose feeding (e.g., up to 500 kcal/day), advancing only as tolerated
 - c. EDEN (2012) (JAMA 2012;307:795-803): 1000 medical ICU patients with acute lung injury (ALI) randomized to receive “trophic” feeds at 10–20 mL/hour versus “full feeds” for the first 6 days of feeding. After 6 days, the feedings were increased to the “full-feeding” rates. Malnourished patients were excluded from study entry. The initial 272 patients were part of the OMEGA study (JAMA 2011;306:1574-81) investigating the influence of fish oil supplementation compared with protein-containing control supplement. The “full-feeding” group received 1300 kcal/day, whereas the “trophic” group received 400 kcal/day. Protein intakes for the groups were not given. There were no differences in clinical outcomes between groups; however, the “full-feeds” group experienced significantly greater GI complications and a higher daily BG concentration.

- d. Two smaller studies (Am J Clin Nutr 2011;93:569-77; Crit Care Med 2011;39:967-74), also implied a benefit from “trophic feeds.” For the Rice study (Crit Care Med 2011;39:967-74), patients received an average of 1418 kcal/day versus 300 kcal/day. No difference was noted in clinical outcomes, but gastric feeding tolerance was improved with the lower caloric intake. However, patients in both groups averaged only 5.5 versus 5.1 days of required EN. Conversely, Arabi (Am J Clin Nutr 2011;93:569-77) provided an average of 1067 kcal/day to the “trophic feeding” group and 1252 kcal/day to the “target feeding” group, a difference of 185 kcal/day (the caloric equivalent of about 1 L of 5% dextrose in water). Their data showed a reduction in 28-day all-cause mortality with permissive underfeeding (23% vs. 18%); however, their data were also confounded by different insulin therapy strategies (target BG 80–110 mg/dL vs. 180–200 mg/dL).
 - e. Dickerson’s interpretation: It is unclear what exact minimum amount of calories and protein are necessary to gain a therapeutic benefit. Early “full” EN and early “trophic” feedings had similar clinical outcomes in the EDEN study, but some clinicians would suggest that this was a comparison of hypocaloric feeding (about 15 kcal/kg/day), not “full feeding” to “trophic” or semi-starvation feeding (about 5 kcal/kg/day). Most clinical studies involving EN in critically ill patients generally achieve intakes of only about two-thirds of what is prescribed for the first week of therapy. Recent efforts for improving EN intake include prokinetic pharmacotherapy, raising of GRV thresholds, and short-term increased EN infusion rates in response to feeding interruptions. These efforts may improve overall caloric and protein intake for “full-feeds” versus “trophic-feeds” comparisons and ultimately provide a clearer answer to this controversial area. Observed differences in clinical outcomes with early EN are likely related to the patient population (e.g., medical ICU vs. surgical/trauma/burn patients), gastric feeding tolerance, duration of EN and ICU stay, actual caloric and protein intakes, and efficacy of glycemic control. The reader is cautioned not to apply the findings from one select patient population (e.g., well-nourished medical ICU patients with acute lung injury) to all critically ill patients.
2. GRVs and prokinetic agents
- a. North American Summit on Aspiration in the Critically Ill Patient (2002) (JPEN J Parenter Enteral Nutr 2002;26(6 suppl):S80-85): GRV of 500 mL or greater indicates need to withhold gastric feeding and reassess tolerance. GRV in the range of 200–500 mL should prompt careful bedside evaluation and initiation of an algorithmic approach to reduce risk.
 - b. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): To reduce the risk of aspiration: Elevate the head of bed 30–45 degrees. GRVs in the range of 200–500 mL should raise concern and lead to the implementation of measures to reduce the risk of aspiration, but automatic cessation of feeding should not occur for GRVs less than 500 mL in the absence of other signs of intolerance.
 - c. REGANE study (Intensive Care Med 2010;36:1386-93): About 300 patients (about 80% medical ICU) were randomized to hold tube feeds for a GRV of 200 mL versus 500 mL. *ALL patients received “prophylactic metoclopramide therapy 10 mg intravenously q8h” for the first 3 days of EN.* Increasing the GRV limit to 500 mL (from 200 mL) was associated with an increase in EN volume received and was not associated with adverse clinical outcomes. There was no difference in days on the ventilator, ICU LOS, mortality, pneumonia (no microbial confirmation was required for the diagnosis of pneumonia), or GI complications between groups.
 - d. Reignier (2013) (JAMA 2013;309:249-56): About 450 patients (more than 90% medical ICU) were randomized to GRV monitoring or no GRV monitoring during EN. Tube feeds were held for GRV greater than 250 mL (in monitoring group) or for vomiting/regurgitation (both groups). No difference was found in ventilator days, ICU or hospital LOS, ICU-acquired infections, or mortality. There was a higher incidence of vomiting (42% vs. 27%) in those without GRV monitoring. Others have suggested that decreased EN delivery may have occurred for the no-GRV

- monitoring group (either intentionally by the over-reporting of emesis/regurgitation or unintentionally by nursing personnel) because there was only a 200-kcal difference in intake between the groups for the week (Nutrition 2013;29:1075-9).
- e. Metheny (2006) (Crit Care Med 2006;34:1007-15): Observational study of 360 patients (around 75% trauma/surgery/neurosurgery/cardiac surgical ICU patients). More patients with pneumonia (n=173) had pepsin-positive tracheal secretions than did those without pneumonia (n=187): 42% vs. 21% (p<0.001). Those with vomiting or diagnosed gastroesophageal reflux disease had more pepsin-positive tracheal aspirates (p=0.01; 0.033). The frequency of aspiration increased for a GRV greater than 250 mL or two consecutive GRVs greater than 200 mL.
- f. Nguyen (2007) (Crit Care Med 2007;35:2561-7; Crit Care Med 2007;35:483-9): Dual metoclopramide/erythromycin therapy is more effective than erythromycin therapy, which is more effective than metoclopramide therapy.
- g. Dickerson (2009) (JPEN J Parenter Enteral Nutr 2009;33:646-55): Combination prokinetic therapy is preferred to metoclopramide therapy alone (because of marked tachyphylaxis) for trauma patients with brain injury; single-drug therapy with metoclopramide is suitable for trauma patients without brain injury.
- h. Dickerson's interpretation: The "key" to interpreting gastric feeding tolerance is routine and frequent abdominal examinations and assessment of the patient for evidence of vomiting, cramping, nausea, regurgitation, or distension. GRV alone as a GI assessment is inadequate and prone to error. Patients with a mild or modestly elevated GRV but a normal abdominal examination or lack of GI symptoms can continue EN. If the patient has symptoms or is distended/tympanic, feedings should be interrupted, and either prokinetic therapy or advancement of the feeding tube into the small bowel should be considered. Also of note, a GRV can sometimes be difficult to accurately assess with a small-bore feeding tube because of the tube collapsing on aspiration or because of its location in the stomach. We empirically prefer this technique to waiting for the patient to regurgitate or vomit because the risk of aspiration increases when these events occur (Crit Care Med 2006;34:1007-15):.
3. Immune-enhancing diets – What makes them unique? Omega-3 fatty acids, glutamine, arginine, nucleotides
 - a. Populations in which their use appears beneficial in reducing infectious complications
 - i. GI cancer surgery (pre- and perioperative)
 - ii. Trauma
 - iii. General surgical?
 - b. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): Immune-modulating enteral formulations should be used for the appropriate patient population (patients with major elective surgery, trauma, burns, and head and neck cancer and those who are critically ill on mechanical ventilation). Surgical patients – grade A; medical ICU patients – grade B. Use with caution in patients with severe sepsis.
 - c. ESPEN EN (2006) (Clin Nutr 2006;25:210-23): Indicated for patients requiring elective upper GI surgery and trauma. Improves outcome in less severe sepsis. Not recommended for patients with severe sepsis or burns
 - d. Surviving Sepsis Campaign guidelines (2013) (Crit Care Med 2013;41:580-637): Suggest using nutrition without specific immune-modulating supplementation
 - e. Dickerson's interpretation: It would make sense not to use an immune enhancing diet (IED) if the patient is already infected because that is the primary goal for using IEDs. Data from patients undergoing GI cancer surgery and trauma patients appear promising. ESPEN guidelines are primarily based on the Galban study (Crit Care Med 2000;28:643-8), which used APACHE II (Acute Physiology and Chronic Health Evaluation II) scores to show the severity of illness/sepsis. Unfortunately, the number of patients in the higher APACHE II-stratified groups was insufficient to show a statistically significant difference (e.g., beta error) in outcomes, despite trends.

4. EN and vasopressors/hemodynamic instability
 - a. The concern: Blood shunting away from the GI tract may predispose patients to reported complications of intestinal ischemia, perforation, and necrosis.
 - b. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): In the setting of hemodynamic compromise (high-dose catecholamines, fluid resuscitation), EN should be withheld until the patient is fully resuscitated and stable.
 - c. Mancl (2013) (JPEN J Parenter Enteral Nutr 2013;37:641-51): Retrospectively evaluated the tolerance and safety of concurrent EN and intravenous vasopressor therapy in 259 patients. An inverse relationship was found between maximum norepinephrine equivalent dose and EN tolerability: 12.5 mcg/minute for patients who tolerated EN compared with 19.4 mcg/minute for those who were intolerant ($p < 0.001$). Serum lactate was elevated in 31% of patients, and 0.9% experienced bowel ischemia or perforation. Tolerability was related to the cumulative vasopressor dose and possibly related to the specific vasopressor administered. The norepinephrine-equivalent dose was 12.5 mcg/minute for those who tolerated EN in contrast to 19.4 mcg/minute for those who did not tolerate EN for the Mancl study.
 - d. Khalid (2010) (Am J Crit Care 2010;19:261-8): A retrospective analysis to evaluate early compared with delayed EN in 1174 critically ill patients who required EN, mechanical ventilation, and vasopressors. Most of the patients were admitted to the ICU for respiratory failure. Unfortunately, few details were given regarding which vasopressor agents were used or what their doses were.
 - e. Dickerson's interpretation: Most cases of intestinal ischemia and bowel perforation during EN with hemodynamic instability stem from surgical or trauma patients in whom intra-abdominal surgery was indicated. Only 6% of the population in the Mancl study were surgical/trauma patients. Although an improvement in cardiac index with pharmacotherapy generally leads to improved splanchnic blood perfusion during shock, most studies suggest—albeit with conflicting data—that epinephrine, norepinephrine, and vasopressin tend to decrease splanchnic blood flow. Intra-gastric administration of EN may be possible for some patients during low, stable doses of vasopressors. However, close monitoring for feeding intolerance is mandatory.
5. EN and pancreatitis
 - a. American College of Gastroenterology guidelines (2013) (Am J Gastroenterol 2013;108:1400-16): In mild acute pancreatitis, oral feeding can be initiated immediately if the patient has no nausea or Am J Gastroenterol 2013;108:1400-16. In severe acute pancreatitis, EN is recommended to prevent infectious complications, whereas PN should be avoided.
 - b. International consensus guidelines (2012) (JPEN J Parenter Enteral Nutr 2012;36:284-91): EN is preferred to PN. EN may be used in the presence of pancreatic pseudocysts, fistulas, and ascites. Early nutrition is indicated for severe pancreatitis. Post-pyloric feeding is not necessarily required. For EN, consider a small peptide-based medium-chain triglycerides (MCT) oil formula to improve tolerance. Use PN if EN is contraindicated or not well tolerated. Intravenous fat emulsions are generally safe and well tolerated as long as the baseline triglycerides are below 400 mg/dL and the patient has no history of hyperlipidemia.
 - c. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): Patients with severe acute pancreatitis should have an NG tube placed and be initiated on EN as soon as fluid volume resuscitation is complete. Patients with mild to moderate acute pancreatitis do not require nutrition support therapy (unless an unexpected complication develops or the patient does not advance to an oral diet within 7 days). Patients with severe acute pancreatitis may be fed by the gastric or jejunal route. For the patient with severe acute pancreatitis, PN use should be considered when EN is not feasible.

- d. Dickerson's interpretation: Most clinicians will try to introduce a low-fat diet or EN formula (with fat content predominantly as MCT) for patients with mild to moderate acute pancreatitis when the abdominal pain and nausea are substantially reduced. Many clinicians will opt for PN for patients with severe acute pancreatitis (with a prolonged course and NPO [nothing by mouth] for a few to several days) if jejunal feeding not possible. When giving EN, a low-fat diet (which includes a substantial portion of the fat kilocalories as MCT) is usually preferred.
6. Fish oil and acute respiratory distress syndrome (ARDS)
 - a. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): Patients with ARDS and severe ALI should be placed on an enteral formulation characterized by an anti-inflammatory profile (i.e., omega-3 fish oils, borage oil) and antioxidants.
 - b. ESPEN EN (2006) (Clin Nutr 2006;25:210-23): Patients with ARDS should receive EN enriched with omega-3 fatty acids and antioxidants.
 - c. Canadian Practice Guidelines update (2014) (Nutr Clin Pract 2014;29:29-43): Downgraded their initial 2009 recommendations from "recommend" (the specialized formula) to "should be considered"
 - d. Rice (2011) (JAMA 2011;306:1574-81): 272 medical ICU patients with ALI/ARDS were randomized to receive either a twice-daily omega-3 supplementation or an isocaloric, protein-containing supplement together with their EN. The supplements were calorically equivalent but differed in protein content (4 g/dose vs. 20 g/dose, respectively). Patients who received fish oil bolus supplements had fewer ventilator-free days (implying worse outcomes) but no difference in mortality or other organ failures compared with those who received the protein control supplement. Those who received fish oil also experienced more diarrhea (29 vs. 21%, respectively). The investigators concluded that twice-daily supplementation of fish oil/ γ -linoleic acid/antioxidant did not improve clinical outcomes and might be harmful.
 - e. Dickerson's interpretation: The first three RCTs (Crit Care Med 1999;27:1409-20; Crit Care Med 2006;34:2325-33; Crit Care Med 2006;34:1033-8) and the subsequent meta-analysis (JPEN J Parenter Enteral Nutr 2008;32:596-605) from those original studies examined a conventional compared with a modified diet for patients with ALI and ARDS. The meta-analysis results showed that the specialized diet improved ICU LOS, ventilator days, organ failure, and mortality compared with the conventional diet. The problem with those studies was that they potentially compared a treatment formula with "the worst formula." In essence, the studies compared the modified diet to another diet of similar high-fat content but as an omega-6 fat source (e.g., the worst formula, given the hypothesis that ARDS is related to the inflammatory process, which can be worsened or improved by the fat source). Rice's data (JAMA 2011;306:1574-81) are difficult to interpret because patients received a bolus supplement in addition to their EN, instead of continuously substituting a portion of the fat kilocalories as fish oil. The control group likely received more protein (40 g/day plus EN) than did the fish oil group (8 g/day plus EN). These patients were also part of the EDEN (JAMA 2012;307:795-803 trial regarding "trophic vs. full feeds," which may have also confounded their data. Because the control group had improved outcomes compared with the fish oil supplement group, it may be asked whether the difference in protein received by the control group contributed to the improved outcome of the control group. Until more data are available, we continue to use a modified diet for patients with ALI and ARDS, even though its benefit was questioned by one RCT.
7. Should lipids be held during the first week of PN?
 - a. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): In the first week of hospitalization in the ICU when PN is required and EN is not feasible, patients should be given a parenteral formulation without soy-based lipids.
 - b. ESPEN PN (2009) (Clin Nutr 2009;28:387-400): Lipid emulsions should be an integral part of PN to provide energy and ensure essential fatty acid provision in long-term ICU patients.

- c. Dickerson's interpretation: The SCCM/ASPEN recommendation was based on a single RCT of 57 trauma patients who received 30 kcal/kg IBW/day in which 25% of the non-protein kilocalories were provided as an intravenous fat emulsion or glucose for the first 10 days of PN (J Trauma 1997;43:52-60). The soybean fat emulsion was infused over a 10- to 12-hour period. Calories lost to the omission of lipid emulsion were not replaced in the control (no-lipid) group, with each group receiving an average of 34 kcal/kg/day compared with 27 kcal/kg/day. Protein intake was maintained at 1.6 g/kg/day. The lipid-containing PN group had more infections, including differences in pneumonia and line sepsis (72 infections in 30 patients), than did the non-lipid group (29 infections in 27 patients). Hospital LOS, ICU LOS, and ventilator days were all greater for the lipid group as well (J Trauma 1997;43:52-60). Short-term (10 hour) infusion of lipid can decrease reticuloendothelial (RES) system clearance after 3 days of intermittent intravenous lipid emulsion infusion at a dosage of 0.13 g/kg/hour (JPEN J Parenter Enteral Nutr 1989;13:614-9). In contrast, continuous infusion of intravenous lipid emulsion at the same total daily dosage was not associated with impaired RES clearance (JPEN J Parenter Enteral Nutr 1990;14:467-71). Unfortunately, serum triglycerides were not measured in the Battistella study (J Trauma 1997;43:52-60). This is important because RES clearance is adversely affected for patients unable to clear the lipid emulsion, as evidenced by hypertriglyceridemia. Some clinicians have also questioned whether overfeeding could have contributed to the observed poorer outcomes. Many clinicians are skeptical of Battistella's findings (J Trauma 1997;43:52-60) and await results from a larger controlled trial. Two recent small retrospective studies have shown no difference in infectious complications after early lipid emulsions (Surg Infect (Larchmt) 2011;12:43-7; Nutr Clin Pract 2014;29:355-9). Most clinicians provide fat emulsion as part of the PN early in the course of the patient's hospitalization.
8. Glutamine
- a. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): Adding enteral glutamine to an EN regimen (not already containing glutamine) should be considered in burn, trauma, and mixed ICU patients. When PN is used in the critical care setting, supplementation with parenteral glutamine should be considered.
- b. ESPEN EN (2006) (Clin Nutr 2006;25:210-23): Glutamine should be added to a standard enteral formula in burn and trauma patients. Data are insufficient to support enteral glutamine supplementation in surgical or heterogeneous critically ill patients.
- c. ESPEN PN (2009) (Clin Nutr 2009;28:387-400): When PN is indicated in ICU patients, the amino acid solution should contain L-glutamine 0.2–0.4 g/kg/day (e.g., alanyl-glutamine dipeptide 0.3–0.6 g/kg/day).
- d. Canadian Practice Guidelines update (2014) (Nutr Clin Pract 2014;29:29-43): When PN is prescribed to critically ill patients, parenteral supplementation with glutamine should be considered (downgraded from "strongly recommended"). We strongly recommend that high-dose glutamine not be used in critically ill patients with shock and multiorgan failure.
- e. REDOX study (2013) (N Engl J Med 2013;368:1489-97): Critically ill patients (n=1223) were randomized to receive placebo, glutamine (0.35 g/kg/day intravenously plus 30 g/day enterally), an antioxidant cocktail (500 mcg of intravenous selenium plus enteral administration of selenium at 300 mcg/day, 20 mg of elemental zinc, beta-carotene, vitamin E, or 1500 mg of vitamin C), or both glutamine and the antioxidant cocktail. One of these treatment regimens was given within 24 hours after admission to the ICU for a maximum of 28 days or until discharge from the ICU. There was a trend toward increased 28-day mortality for those who received glutamine compared with those who did not (32% vs. 27%; adjusted odds ratio of 1.28, p=0.05). Antioxidants had no effect on 28-day mortality.

- f. Dickerson's interpretation: The REDOXS study showed that aggressive glutamine dosing might be harmful when used in the critically patient with multiple organ dysfunction (40% of patients had renal dysfunction). The glutamine dose was about 0.7–0.8 g/kg/day for many patients, which exceeded the 0.3- to 0.5-g/kg/day doses that previously were shown to be of benefit (Crit Care Med 2003;31:2444-9; Crit Care Med 2001;29:2075-80). The REDOXS data may have also been skewed because the number of patients with more than two failing organs at baseline was higher in the groups receiving glutamine than in those not receiving glutamine (187 vs. 148), which likely contributed to a higher mortality. In addition, 79% of the patients were medical ICU patients. The current body of literature suggests that glutamine supplementation appears to be beneficial for thermally injured and trauma patients (Nutr Clin Pract 2011;26:479-94). Only 3% of the study population were trauma patients, and those with significant thermal injury were excluded. Because of the unfavorable results obtained in the REDOXS study, the principal investigator in a separate publication recommended that glutamine supplementation be reserved for trauma or thermally injured patients at a dosage of 0.35–0.5 g/kg/day (JPEN J Parenter Enteral Nutr 2013;37:442-3). It is also recommended that glutamine administration be avoided in patients with significant renal or hepatic dysfunction.
9. Selenium
 - a. SCCM/ASPEN (2009) (JPEN J Parenter Enteral Nutr 2009;33:277-316): A combination of antioxidant vitamins and trace minerals (specifically including selenium) should be provided to all critically ill patients receiving specialized nutrition therapy.
 - b. ESPEN PN (2009) (Clin Nutr 2009;28:387-400): All PN prescriptions should include a daily dose of multivitamins and trace elements. Selenosis has been observed in the healthy population with long-term intakes greater than 750 mcg/day; therefore, doses of 750–1000 mcg/day should probably not be exceeded in the critically ill, and administration of supraphysiologic doses should perhaps be limited to 2 weeks.
 - c. Surviving Sepsis Campaign guidelines (2013) (Crit Care Med 2013;41:580-637): Use of selenium to treat severe sepsis is not recommended.
 - d. Canadian Practice Guidelines update (2014) (Nutr Clin Pract 2014;29:29-43): Given the outcome of reduced infections, evidence is sufficient to upgrade the recommendation for the use of intravenous/PN selenium supplementation from “insufficient data” to “should be considered.”
 - e. Dickerson's interpretation: Although the emerging data look promising (excluding the REDOXS trial), one problem is the practicality of delivering selenium therapy to non-infected critically ill patients. Most studies that showed improved outcomes administered a bolus selenium dose, followed by a continuous insulin infusion. Because many critically ill patients require other continuous infusions (fentanyl/midazolam/insulin/vasopressors/propofol, PN), the practicality of providing all of these infusions is complex given the availability of ports for infusion. In addition, there is the problem of inadequate dosing information in AKI or renal insufficiency. Thus, given selenium's emerging but not universally accepted proof of benefit, it has become more of a quagmire regarding what to do with selenium, and selenium is not usually provided beyond conventional doses in PN solutions at many institutions.
10. Arginine: There is a risk of arginine causing hypotension because it is a precursor to the vasodilator nitric oxide. In one small study of vasopressor-dependent critically ill patients with infections, an intravenous bolus dose of 200 mg/kg of L-arginine resulted in transient hypotension and hemodynamic changes that lasted for 10–15 minutes (Crit Care Med 1993;21:1287-95). However, given the amount of arginine contained in nutritional formulations and its method of delivery (continuous infusion), it is unlikely that EN and PN solutions could significantly contribute to hemodynamic instability (Nutr Metab (Lond) 2012;9:54). In addition, the use of arginine-supplemented enteral diets has been shown to improve infectious complications and decrease hospital LOS when used perioperatively for patients requiring GI surgery (J Am Coll Surg 2011;212:385-99).

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D

Hyperglycemia and other causes of non-hypotonic hyponatremia have been excluded. Urine osmolality is greater than 100 mOsm/kg, which rules out psychogenic polydipsia, and a large amount of hypotonic fluids were not being given. Urine sodium was greater than 30 mEq/L, and the patient did not receive diuretic therapy or have kidney disease. The patient appeared to be normovolemic without evidence of significant edema (expansion of the ECF compartment). Because the patient also has pneumonia (a common cause of SIADH), all of these factors indicate that the patient has hyponatremia caused by SIADH.

2. Answer: B

Fluid restriction in which excess water is retained relative to sodium is the most appropriate treatment of SIADH. The “vaptans” may also be considered; however, this was not a choice.

3. Answer: D

The best way to fluid-restrict an enterally fed patient is to use the most concentrated formulas, which are the 2-kcal/mL formulations that are specifically designed for patients with congestive heart failure. Unfortunately, protein intake may be inadequate with the use of these formulations in certain populations, and supplemental protein may have to be provided.

4. Answer: D

These dosages should be selected as the correct answer as they follow the dosing guidelines. However, in practice, because this patient is at risk of refeeding syndrome (substantial recent weight loss) and hypophosphatemia (weight loss, glucose-based PN solution, liver resection), a more aggressive dosing approach would probably be better. Because he has an NG volume output of 2 L, enteral administration of electrolytes would not be practically feasible. Supplemental potassium and phosphorus would be added to the PN solution, in addition to daily intravenous doses of potassium and phosphorus.

5. Answer: B

Because it takes about 48 hours for serum magnesium to redistribute, the next day’s serum magnesium concentration is “falsely elevated.” In general, it will

take about 4–5 days to replete this patient’s magnesium deficiency (presumably caused by chronic alcohol ingestion). Supplemental magnesium would be added to the PN solution in addition to daily doses of intravenous magnesium sulfate.

6. Answer: C

Although critical illness and fluid resuscitation therapy may have factored into the development of his hypocalcemia, massive blood transfusion is the most profound cause. Citrate, added to the blood as an anticoagulant, readily binds calcium and can cause hypocalcemia. Previous studies have shown that hypocalcemia is common when patients are given more than 5 units of blood at a time.

7. Answer: B

A short-term intravenous infusion of 4 g of calcium gluconate (1 g = 4.6 mEq) over 4 hours has previously been shown to be a safe and effective therapeutic regimen for moderate to severe hypocalcemia (ionized calcium less than 1 mmol/L). A bolus dose of calcium chloride (1 g = 13.6 mEq) would be an effective means for treating symptomatic hyperkalemia, but it would be unnecessarily aggressive in this patient scenario.

8. Answer: A

Calculation of the AG ($141 + 4 - 117 - 21 = 7$) shows that no AG is present. The pH of 7.29 with a low-normal P_{CO_2} suggests mild metabolic acidosis. Respiratory compensation should have been better, but this may not be possible for the patient, depending on the ventilator settings. The serum chloride of 117 mEq/L indicates hyperchloremia. A non-AG hyperchloremic metabolic acidosis is common for patients with an ileal conduit where urine is diverted into a short loop of ileum (urinary chloride reabsorption occurs) that acts as ostomy for urine output.

9. Answer: A

Because the severity of the patient’s acidemia is mild (pH 7.29), aggressive therapy with sodium bicarbonate is not indicated. In addition, sodium bicarbonate is incompatible with calcium-containing PN solutions and cannot be added to the PN solution. Calculation of the bicarbonate deficit ($0.5 \times 50 \times (24 - 21) = 75$ mEq)

suggests that changing the sodium chloride to sodium acetate would correct the bicarbonate deficit within 24–48 hours. However, patients with ileal conduits tend to have persistent hyperchloremic metabolic acidosis (likely from other chloride solutions given to the patient, which are then excreted in the urine and reabsorbed in the ileal conduit), and more prolonged therapy may be required.

10. Answer: C

The current PN regimen provides 61 kcal/kg/day total (glucose 6.1 mg/kg/minute and lipid emulsion 1.5 g/kg/day) and protein 4 g/kg/day. The PN regimen represents gross overfeeding of this small woman and can explain her hyperglycemia and hypercapnia. Cutting all macronutrients by about one-half would result in a more reasonable regimen for this patient: 30 kcal/kg/day (glucose 3 mg/kg/minute and lipid emulsion 0.8 g/kg/day) and protein 2 g/kg/day. Because she is so small (40 kg), it would be important to double-check the weight-based calculation to see whether this new regimen is appropriate to meet her caloric needs without overfeeding by calculating the BEE using the Harris-Benedict equation for females (caloric intake should not exceed $1.3\text{--}1.5 \times \text{BEE}$ for a critically ill patient with traumatic injuries).

11. Answer: A

Total kilocalories per day = $(200 \text{ g} \times 3.4 \text{ kcal/g dextrose}) + (150 \text{ g} \times 4 \text{ kcal/g protein}) + (50 \times 10 \text{ kcal/g lipid emulsion}) = 1780 \text{ total kcal/75 kg} = 23.7 \text{ kcal/kg IBW/day} = 24 \text{ kcal/kg IBW/day}$. Protein intake is $150 \text{ g/75 kg} = 2 \text{ g/kg IBW/day}$. This caloric and protein intake would be appropriate for hypocaloric, high-protein nutrition therapy in critically ill patients with obesity without significant renal or hepatic dysfunction.

12. Answer: C

$N_{in} = 150 \text{ g of amino acids}/6.25 = 24 \text{ g}$.
 $UUN = 900 \text{ mg/dL} = 9 \text{ g/L}; 9 \text{ g/L} \times 3 \text{ L} = 27 \text{ g}$.
 $NB = 24 - 27 - 4 = -7$.

13. Answer: B

In an effort to avoid overfeeding yet meet the demands of increased catabolism, the appropriate modification of the PN formulation is to increase the protein content while decreasing the non-protein energy content. Increasing the protein intake from 150 g to 190 g/day (around 2.5 g/kg IBW/day) will provide an additional

6.4 g of nitrogen, which should place the patient close to nitrogen equilibrium (assuming that most of the additional nitrogen is retained). Increasing the protein intake without altering the non-protein intake will increase the total caloric intake to 26 kcal/kg/day. If the goal is to keep the caloric intake the same at around 24 kcal/kg IBW/day, reducing the fat intake to 35 g/day (from 50 g/day) would meet that goal.

14. Answer: A

Because the target BG should be 140–180 mg/dL for this surgical patient being transferred to the floor, a modest improvement in glycemic control is indicated. Ideally, obligatory glucose requirements should be met (e.g., about 130 g/day plus about 80–150 g/day for wound healing) to prevent the use of amino acids for gluconeogenesis. Thus, decreasing the glucose intake to 100 g/day is not desirable, given the mild increases in BG concentration. The easiest method to achieve glycemic control and meet caloric needs is to modestly increase the regular human insulin by 10 units/day. The patient is unlikely to experience hypoglycemia with the provision of insulin at 30 units/day when given 200 g of intravenous dextrose concurrently. As the stress resolves and glycemic control improves, insulin can be decreased or eliminated from the PN solution.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: C**

An ileus, usually detected on radiologic examination of the lower abdomen, indicates lack of motility and presence of distention and air within the small bowel. This is usually depicted as “dilated loops of bowel.” Patients cannot be fed safely or efficaciously by the enteral route during an ileus. A feeding tube can be placed for enteral feeding of the patient with anorexia, and PN is not indicated. Presence or absence of bowel sounds is not an accurate marker for assessing bowel function. A high GRV during enteral feeding, combined with abdominal distension, bloating, emesis, or regurgitation, can often be efficaciously treated with prokinetic pharmacotherapy or advancement of the feeding tube into the small bowel with resumption of enteral feeding.

2. Answer: B

The correct answer is B, “0.45% sodium chloride and potassium chloride 20 mEq/L,” based on the average electrolyte composition of gastric fluid (see Table 5 regarding the electrolyte composition of GI fluids).

3. Answer: A

With significant diarrhea, intravenous zinc requirements from GI fluid losses during critical illness will increase from the normal requirements of 3–5 mg/day. Data show that most patients with increased intestinal losses can achieve a positive zinc balance on 13 mg of intravenous zinc daily (*Gastroenterology* 1979;76:458-67). As a result, most clinicians will provide additional zinc supplementation for patients with short bowel syndrome, intestinal fistulas, or prolonged and sustained diarrhea.

4. Answer: C

Given the severity of the patient’s condition (recent seizure from severe hyponatremia) and likely diagnosis of syndrome of inappropriate diuresis or SIADH. The immediate goal should be to achieve a serum sodium concentration of greater than 120 mEq/L by short term infusion of 3% sodium chloride. Conivaptan could then be given to correct the hyponatremia limiting the increase in serum sodium concentration to less than 10–12 mEq/L/day. Fluid restriction is imperative and is the primary overall management technique for this patient.

5. Answer: B

Studies show that increases in mesenteric potassium concentrations detected by potassium sensors in the splanchnic vascular bed evoke increased renal potassium excretion (feed-forward regulation of potassium homeostasis), even before regulation by aldosterone (classic feedback regulation). Some clinicians may have erroneously selected bioavailability, but the bioavailability of enteral potassium is 95%–100% in the absence of aberrations in GI motility, function, or anatomy. A major difference between enteral and parenteral potassium is that the rate of absorption is slower with enteral potassium. The rate of intravenous potassium administration can be inadvertently infused too quickly (it is acceptable to infuse potassium at 10 mEq/hour for patients without a cardiac monitor and up to 20 mEq/hour for those with a monitor).

6. Answer: C

Folic acid deficiency is correct because the patient’s homocysteine concentration is elevated, whereas her methylmalonic acid concentration is normal. If both were elevated, it would likely be a vitamin B12 deficiency, although a combined B12-folate deficiency is possible (but less common than a B12 deficiency alone). If her methylmalonic acid concentration were elevated and her homocysteine were normal (rare), she would likely have a vitamin B12 deficiency. If both are normal, the patient’s macrocytosis is caused by other factors such as liver disease or alcohol.

7. Answer: D

The correct answer is D, “additional magnesium therapy should be given daily over the next 4–5 days,” because it takes 48 hours for magnesium to equilibrate after a short-term infusion. Treatment of significant hypomagnesemia usually takes a few to several days of repletion therapy. Hypocalcemia should autocorrect with magnesium supplementation with 48 hours of magnesium therapy, but calcium therapy can be given concurrently, if necessary (symptomatic or ionized calcium concentration less than 1 mmol/L).

8. Answer: B

Described are the calculations for determining an NB:

$$\text{NB} = \text{N}_{\text{in}} - \text{UUN} - 4$$

$$\text{N}_{\text{in}} = \text{protein in (g/day)} / 6.25 = 20.8 \text{ g}$$

$$\text{UUN (g/day): } 900 \text{ mg/dL} = 9000 \text{ mg/dL} = 9 \text{ g/L; } 2700 \text{ mL/day} = 2.7 \text{ L/day}$$

$$9 \text{ g/L} \times 2.7 \text{ L/day} = 24.3 \text{ g/day}$$

$$\text{NB} = 20.8 - 24.3 - 4 = -7.5 \text{ g/day}$$

If asked, “what adjustments would you make to the parenteral nutrition regimen?”, the best choice would be to increase the protein intake (to about 2 g/kg/day) because the current regimen provides only around 1.4 g/kg/day. Although the NB is usually negative for a critically ill patient because the anabolic effect of nutrition cannot completely overcome the catabolism of critical illness, most patients can achieve close to nitrogen equilibrium (an NB of around -4 to +4 g/day). Increasing the protein intake by 50 g/day should provide about 8 g of additional nitrogen, which should be sufficient to achieve an NB close to nitrogen equilibrium.