**GI/Liver/Nutrition PRN Focus Session—Contemporary Issues in the Management of Total Parenteral Nutrition**
Activity No. 0217-0000-11-100-L01-P (Knowledge-Based Activity)

**Tuesday, October 18**
3:30 p.m.–5:30 p.m.
Convention Center: Rooms 302 & 303

*Moderator: Joseph V. Ybarra, Pharm.D., BCNSP*
Assistant Clinical Professor, Harrison School of Pharmacy, Auburn University, Auburn, Alabama

**Agenda**

| | |
|---|---|
| 3:30 p.m. | Management of TPN in Patients with Kidney Disease<br>*Sarah Nordbeck, Pharm.D., BCNSP*<br>Nutrition Support Pharmacy Specialist, Beaumont Hospital, Northville, Michigan |
| 4:05 p.m. | Management of TPN in Patients with Obesity<br>*Erin Nystrom, Pharm.D., BCNSP*<br>Clinical Specialist in Nutrition Support, Assistant Professor of Medicine, College of Medicine, Mayo Clinic, Rochester, Minnesota |
| 4:40 p.m. | Micronutrient Supplementation and Long-term Adverse Effects of TPN Therapy<br>*Leslie Hamilton, Pharm.D., BCPS*<br>Assistant Clinical Professor, Department of Pharmacy Practice, Auburn University, Birmingham, Alabama |
| 5:15 p.m. | Panel Discussion<br>*Leslie Hamilton, Pharm.D., BCPS*<br>*Sarah Nordbeck, Pharm.D., BCNSP*<br>*Erin Nystrom, Pharm.D., BCNSP* |

**Faculty Conflict of Interest Disclosures**

Leslie Hamilton: no conflicts to disclose.
Sarah Nordbeck: no conflicts to disclose.
Erin Nystrom: no conflicts to disclose.

**Learning Objectives**

1. Review current recommendations for dosing and monitoring of TPN in patients with acute, chronic, and end stage kidney disease.
2. Discuss the management of TPN in patients undergoing hemodialysis or continuous renal replacement therapies.

3. Discuss potential complications of TPN therapy in patients with chronic or end stage kidney disease.
4. Review the appropriate roles for both acute and chronic TPN therapy in obese patients.
5. Provide recommendations for dosing and monitoring of TPN in patients with obesity.
6. Discuss potential complications of TPN therapy in patients with obesity.
7. Review the role and appropriateness of micronutrient supplementation in patients receiving TPN therapy.
8. Provide recommendations for dosing and monitoring of micronutrient supplementation in acute and chronic TPN therapy.
9. Discuss strategies for prevention and management of long term adverse effects of TPN therapy.

**Self-Assessment Questions**

Self-assessment questions are available online at *www.accp.com/am*


# Management of TPN in Patients with Kidney Disease

***Sarah Nordbeck, Pharm.D., BCNSP***

Nutrition Support Pharmacy Specialist, Beaumont Hospital, Northville, Michigan

## Conflicts of Interest

American College of Clinical Pharmacy

# No conflicts to disclose

# Learning Objectives

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- Review current recommendations for dosing and monitoring of TPN in patients with acute, chronic, and end stage kidney disease.
- Discuss the management of TPN in patients undergoing hemodialysis or continuous renal replacement therapies.
- Discuss potential complications of TPN therapy in patients with chronic or end stage kidney disease.

# KDOQI

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- Kidney Disease Outcomes Quality Initiative
  - 26 million Americans have CKD
  - 367,000 with ESRD on dialysis
  - Approximately 600,000 cases of AKI annually

Kidney International 2011; 79:1361–1369;79.

# Acute Kidney Injury

- Mortality remains > 50%
  - Causes of AKI:
    - Sepsis
    - Trauma
    - Hypotension
    - Contrast dye
    - Medications
    - Pre-existing CKD

ASPEN 2010 Guidelines.
JAMA. 2005;294:313-318
Am J Med. 2005;118:827-832

# Causes of AKI

- Prerenal
  - Hypoperfusion
- Intrinsic
  - Damage to the renal parenchyma
- Postrenal
  - Urinary obstruction

Am Fam Physician. 2000 Apr 1;61(7):2077-88.
.

# Patient Case

- 63 yo female admitted on 10/15/09 for pneumonia, severe metabolic acidosis

- PM/SH:  ESRD on M/W/F on HD, a fib, metabolic acidosis, depression, gastric bypass in 1999.

- Nutrition hx:
  - 5'3"
  - Admit wt: 67.3 kg
  - IBW: 52.4 kg

+ 3 edema

Chronic diarrhea

Pre-albumin < 5

# Pt case – initial TPN order

- 2400 ml fluid
- 150 g dextrose
- 20 g fat
- 75 g protein
- 100 meq Na-acetate
- 20 meq Na-phos
- 40 meq K-acetate
- 20 meq Ca Gluconate
- 16 meq Mag Sulfate
- 1 mL Trace Element
- 10 mL MVI
- Thiamine 100 mg
- Zinc chloride 10 mg

# Metabolic Alterations in AKI

- Metabolic acidosis
  - Inability to excrete H+ from distal tubule
  - Inadequate bicarbonate synthesis and reabsorption
  - Decreased ammonia production
  - Depletion of available buffers
  - Lactate production

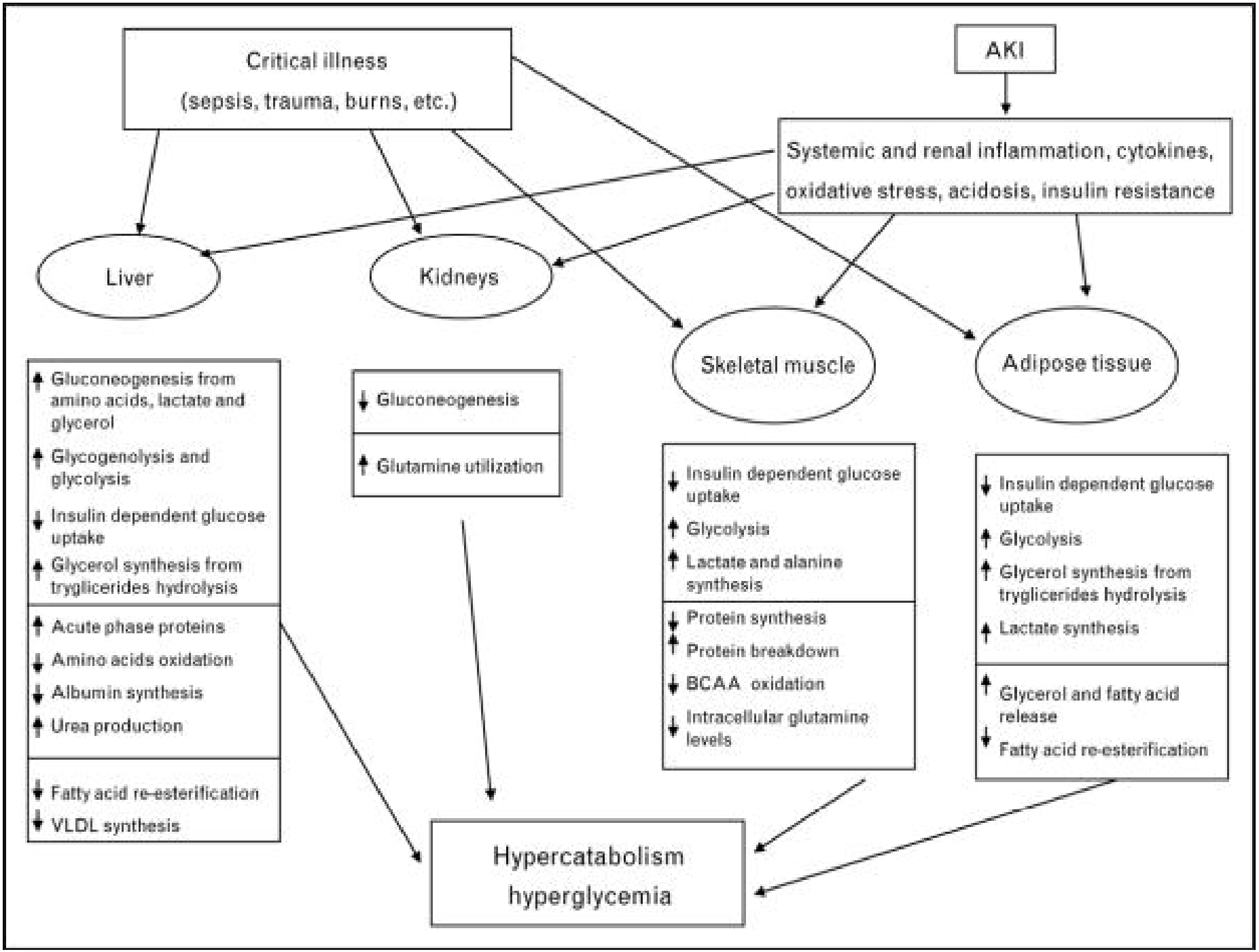
Nutrition in Clinical Practice 20: 176-191, April 2005.

# Metabolic Alterations in AKI

- Fluid/electrolyte abnormalities
  - Hyperkalemia
  - Hyperphosphatemia
  - Fluid overload
  - Azotemia
  - Calcium derangements

- Hypercatabolism
  - Glucose intolerance

Nutrition in Clinical Practice 20: 176-191, April 2005.


Critical illness
(sepsis, trauma, burns, etc.)
AKI
Systemic and renal inflammation, cytokines,
oxidative stress, acidosis, insulin resistance
Liver
Kidneys
Skeletal muscle
Adipose tissue
Gluconeogenesis from amino acids, lactate and glycerol
Glycogenolysis and glycolysis
Insulin dependent glucose uptake
Glycerol synthesis from tryglicerides hydrolysis
Acute phase proteins
Amino acids oxidation
Albumin synthesis
Urea production
Fatty acid re-esterification
VLDL synthesis
Gluconeogenesis
Glutamine utilization
Insulin dependent glucose uptake
Glycolysis
Lactate and alanine synthesis
Protein synthesis
Protein breakdown
BCAA oxidation
Intracellular glutamine levels
Insulin dependent glucose uptake
Glycolysis
Glycerol synthesis from tryglicerides hydrolysis
Lactate synthesis
Glycerol and fatty acid release
Fatty acid re-esterification
Hypercatabolism
hyperglycemia

# Protein Energy Wasting

- Occurs in up to 40% of AKI patients
- Associated with
  - Major stress-induced hormonal and metabolic derangements
  - Clearance of most amino acids up to 1.3-1.8 g/kg/day
  - Negative nitrogen balance
  - Depletion of body energy stores
- Poor outcomes:
  - Loss of lean body mass
  - Increase LOS
  - Increase sepsis, bleeding, arrythmia, resp failure
  - Delayed wound healing

Current Opinion in Critical Care 2009,15:474-480
JPEN 2011,35: 217-222.

# Goals of Nutrition Therapy

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- Provide exogenous fuels to attenuate catabolism thereby maintaining lean body mass.
- Maintenance nutritional status
- Avoidance of worsening metabolic derangements
- Improve wound healing
- Support immune function
- Attenuate inflammation

Current Opinion in Critical Care 2009,15:474-480.
ASPEN 2010 Guidelines

# Tools for evaluating nutrition status

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- Albumin
- Pre-albumin
- Lymphocyte count
- BW changes
- Muscle wasting by anthropometrics
- Energy expenditure (EE)

Current Opinion in Critical Care 2009,15:474-480.

# Subjective Global Assessment

*(Select appropriate category with a checkmark, or enter numerical value where indicted by "#".)*

A. History

1. Weight change
   Overall loss in past 6 months: amount = # _____ kg; % loss = # _____
   Change in past 2 weeks _____ increase,
   _____ no change,
   _____ decrease.

2. Dietary intake change (relative to normal)
   _____ No change
   _____ Change _____ duration = # _____ weeks.
   _____ type: _____ suboptimal solid diet, _____ full liquid diet
   _____ hypocaloric liquids, _____ starvation.

3. Gastrointestinal symptoms (that persisted for >2 weeks)
   _____ none, _____ nausea, _____ vomiting, _____ diarrhea, _____ anorexia.

4. Functional capacity
   _____ No dysfunction (eg, full capacity),
   _____ Dysfunction _____ duration = # _____ weeks.
   _____ type: _____ working suboptimally,
   _____ ambulatory.
   _____ bedridden.

5. Disease and its relation to nutritional requirements
   Primary diagnosis (specify) _____
   Metabolic demand (stress): _____ no stress, _____ low stress,
   _____ moderate stress, _____ high stress,

B. Physical (for each trait specify: 0 = normal, 1+ = mild, 2+ = moderate, 3+ = severe).
   # _____ loss of subcutaneous fat (triceps, chest)
   # _____ muscle wasting (quadriceps, deltoids)
   # _____ andkle edema
   # _____ sacral edema
   # _____ ascites

C. SGA rating (select one)
   _____ A = well-nourished
   _____ B = moderately (or suspected of being) malnourished
   _____ C = severely malnourished

# 2010 ASPEN Guidelines

- Standard amino acid parenteral formulas should be used in AKI (Grade: C)

- Intradialytic parenteral nutrition **should not be used** as a supplement in malnourished CKD-V hemodialysis patients (Grade:C)

Journal of Parenteral and Enteral Nutrition 34;366-377:July 2010.

# 2010 ASPEN Guidelines

- Renal failure patients requiring nutrition support should receive enteral nutrition if intestinal function permits (Grade: E)

- Energy requirements in patients with renal disease should be evaluated using **indirect calorimetry** when possible. If not possible, individualized assessment of energy intake goals is recommended. (Grade: D)

# 2010 ASPEN Guidelines

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- To promote positive nitrogen balance in patients with AKI, protein intake should be adjusted according to catabolic rate, renal function, and dialysis losses

  (Grade D)

- Electrolyte intake in patients should be adjusted by monitoring serum concentrations of K, Mg, P, and Ca

  (Grade D)

# Indications for Nutritional Support

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"Individuals undergoing maintenance dialysis who are unable to meet their protein and energy requirements with food intakes for an extended period of time should receive nutrition support"

"If tube feedings are not used, intradialytic parenteral nutrition (IDPN; for hemodialysis) should be considered"

KDOQI Nutrition Guidelines. 2011.

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# So how do we accomplish this ?

# Dialysis Modalities

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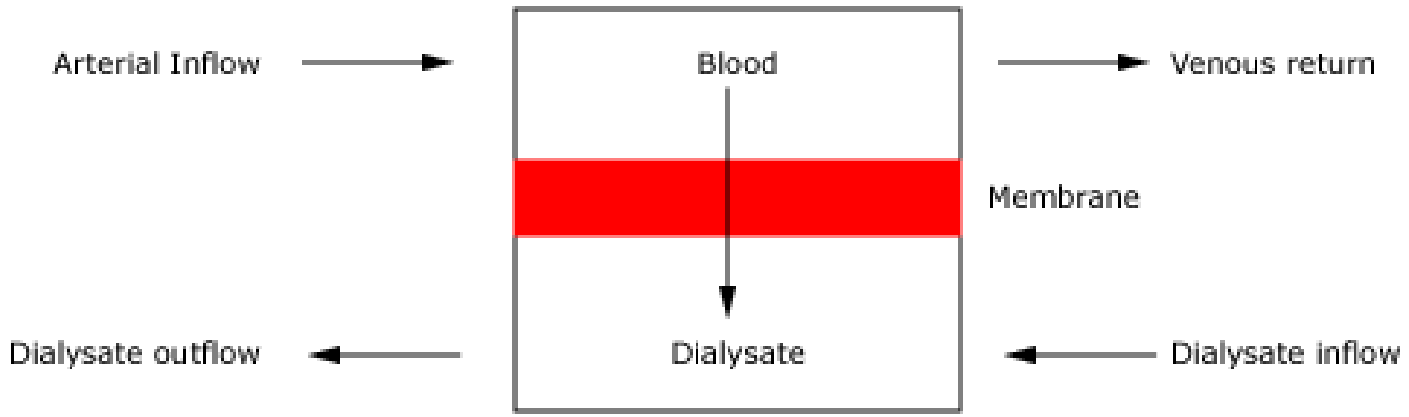
- Intermittent hemodialysis (HD)
- CAPD
- CRRTs

# Intermittent Hemodialysis

- Typically 3-4 hour session three times weekly
- Diffusion

## Solute movement in dialysis




Schematic representation of the movement of solute from blood to dialysate across the dialysis membrane. Blood and dialysate move in opposite directions (ie, flow in a countercurrent fashion) to maximize the clearance of solute.

## Concentrations of dialysate components used in hemodialysis

| | |
|---|---|
| Sodium (meq/L) | 135 to 155 |
| Potassium (meq/L) | 0 to 4 |
| Calcium (mmol/L) | 1.25 to 1.75 (2.5 to 3.5 meq/L) |
| Magnesium (mmol/L) | 0 to 0.75 (0 to 1.5 meq/L) |
| Chloride (meq/L) | 87 to 120 |
| Bicarbonate (meq/L) | 25 to 40 |
| Glucose (g/dL) | 0 to 0.20 |

*Data from Van Stone, JC. Hemodialysis: Hemodialysis apparatus. In: Handbook of Dialysis Daugirdas, JT, Ing, TS (Eds), Little, Brown, Boston, 1994. p. 53.*

# Continuous renal replacement therapies

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- Proposed advantages over intermittent procedures:
  - Better hemodynamic stability
  - Slow volume shifts
  - Progressive elimination of urea
  - Possible elimination of inflammatory mediators

JPEN 2011; 35: 217-222.

# CRRTs

- Continuous venovenous hemofiltration (CVVH)
- Continuous filtration of blood via a pump using the vein as entry and exit
- Convection/solvent drag

JPEN 35:217-222, 2010.
NCP 20:176-191, April 2005.

# Replacement Fluids

| | Na | K | Ca | Cl | HCO3 | Lactate | Mg | Glucose (mg/dL) |
|---|---|---|---|---|---|---|---|---|
| #1 | 130 | 2 | 0 | 108.5 | 25 | 0 | 1.5 | 100 |
| #2 | 130 | 4 | 0 | 110.5 | 25 | 0 | 1.5 | 100 |
| #3 | 140 | 4 | 3 | 113 | 35 | 0 | 1 | 100 |

# Protein losses in RRT

- Higher losses in convection techniques
- Amino acid losses up to 15 grams/day
- Nitrogen balance highly correlated with protein intake

JPEN 35:217-222, 2010.
NCP 20:176-191, 2005.
Nutrition 19:909-916, 2003.

# ASPEN Core Curriculum 2007
# Energy Requirements

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- Harris-Benedict
  - ABW vs. IBW vs. TBW?
- Stable renal failure
  - 20-30 kcals/kg
- AKI
  - 25-35 kcals/kg
    - or 1.3 X the REE
  - Indirect calorimetry

# Energy requirements during acute illness

- Acutely ill maintenance dialysis patients should receive > 35 kcal/kg/day for those < 60 years of age

- 30-35 kcals/kg/day for those > 60 years of age

# Historic practice

- Late 80s and early 90s, practice was < 1 g/kg/day and 30-45 kcals/kg

- Recommended energy intakes for AKI patients have progressively lowered to 25-30 kcals/kg per day and higher amounts of protein

Nutrition in Clinical Practice 26;143-150:2011.

# Recommended amount of protein during acute illness

- 1.8-2.5 g/kg for CRRT
- AKI requiring HD 1.5 g/kg
- 1.2 g/kg for stable ESRD on HD
- 1.3 g/kg for CAPD

Nutrition. 2003;19:909-916.
Nephrol Dial Transplant. 2005 Sep;20(9):1976-80.
ASPEN 2010.
2011 K DOQI Guidelines.

# Fluid and Sodium

- Must be monitored closely in all RF patients
- Anuric pts
  - (urine output < 75 mL/day) are typically restricted to 1000 – 1500 mL/day
- Oliguric patients
  - (urine output < 400 ml/day) can tolerate a bit more fluid
  - < 2 liters/day
- CRRTs even more removal
  - No fluid restriction

# Effects on Electrolytes

- Potassium, magnesium, phosphorus accumulate in renal failure

- Calcium-phosphate precipitation
  - More problematic in chronic dialysis patients
  - Concern for calciphylaxis
  - Keep calcium phosphate product < 55

# Vitamin Requirements

- Not well established in renal pts
- Standard additives
- Vitamin C
  - Limit to < 200 mg/day
- Fat soluble vitamins

Nutrition in Clinical Practice 20:176-191, 2005.

# Chronic Kidney Disease

- Estimated 10% of ESRD pts are severely malnourished
  - 33% are moderately malnourished
- Serum albumin < 3.5 mg/dL
  - 2x mortality than albumin > 4
- Serum albumin < 2.5
  - linked to 10 fold increase in mortality.

Am J Health-Sys Pharm. 2002. 59:1736-1741.
Am J Kidney Dis. 1990;15:458-82.

# Chronic Kidney Disease

- Balanced energy requirements
  - Protein 10-15% total calories
  - Carbohydrate 55-70% calories
  - Fat 20 -30% of calories
- Avoid excessive lipid calories due to diminished clearance rates
- Fluid restriction for oliguria or anuria
- Must account for glucose from PD

# Chronic Kidney Disease MDRD trial

- Low protein (0.6-0.8g/kg) historically used to reduce uremia
  - Intended to slow the progression of renal disease
- Intent to treat analysis  following 585 patients with CKD
  - Disease progression in Stage 3 or 4 patients not slowed by dietary protein restriction to 0.3 or 0.6 g/kg/day when compared to 1.3 g/kg

Kidney International, 51:1908-1919, 1997.

# Protein Restriction

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- Practice used for stages 1 - 4 CKD to postpone kidney disease progression
- Concern for malnutrition when extended over a period of time

KDOQI 2011.
NCP 2011;26:143-150.

# Adult Renal Failure PN Requirements

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| | Pre-dialysis | PD | HD/CRRT |
|---|---|---|---|
| Energy | CRF/ARF: Harris Benedict | ARF:<br>Stress factor 1.5 - 2<br>CRF:<br>Stress factor 1.1 – 1.2 | Same |
| Protein | 0.6-0.8 g/kg | 1.2-1.3 g/kg<br>Up to 1.5-1.8 g/kg for ARF | 1.2 – 1.3 g/kg ESRD<br>1.5-1.8 for ARF on HD<br>1.5-2.5 for CRRTS |
| Fluid | As tolerated | As tolerated | As tolerated |
| Electrolytes<br>Na<br>K | 35-75 mEq/L<br>10-40 mEq/L | Same | Same |

2007 ASPEN Core Curriculum

# Patient case revisited…

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- Patient on TPN x 2 weeks then discharged home

- Re-admitted 7 days later
  - Nephrologist orders intra-dialytic TPN
    - concern for malabsorption
    - no central line due to risk of infection

# Intradialytic PN

- Provides 1000-1200 kcals/treatment
- For patients who cannot tolerate or have not responded to enteral supplements
- Indicated:
  - Serum albumin < 3.4
  - Dietary protein intake < 0.8 g/kg
  - Dietary intake < 25 kcals/kg/day

Am J Kidney Dis. 1999;33:211-6.

# Efficacy of Intradialytic PN

- 4 studies demonstrate weight gain and improved serum albumin
  - Adverse events: Excess fluid gain
    Hyperglycemia

Am J Kidney Dis. 1994;23:808-816
Am J Kidney Dis 1994;24:912-920.
Am J Health-Syst Pharm. 2002;59:1736-41.
J Renal Care. 2008;34:14-18.

# Efficacy of Intradialytic PN

- Cano et al.
  - Prospective study n = 186
  - IDPN + oral supplements n = 93
  - Oral supplements alone n = 93
- Primary endpoint
  - **No difference in mortality at 2 years**
  - 36 deaths in control group
  - 40 in IDPN group

J Am Soc Nephrol 18: 2583-2591, 2007.

# Intradialytic TPN order

- 400 cc/hr x 3 hrs during HD three times weekly
  - 100 grams dextrose
  - 20 grams fat
  - 100 grams protein — Total 940 kcals/session
  - Continues on intra-dialytic TPN for 4 months
    - HD session increased to 4 hours due to fluid overload

# Complications of Parenteral Nutrition

- Refeeding syndrome
- Overfeeding
  - Increased CO2 production, respiratory acidosis
- Hyperglycemia
- Electrolyte abnormalities
- Fluid overload
- Azotemia

Am J Health-Sys Pharm 61;1938-1949:2004.

# Patient case

- Pt re-admitted with malabsorption, calciphylaxis
- Physician requests daily TPN while admitted
- Daily TPN x 2 weeks until patient is febrile
- BC x 2 drawn
  - 2/2 + GPC
- TEE negative to r/o endocarditis
- Transfer to ICU for traumatic pneumothorax, intubated, CRRTs started
- Patient recovered and discharged home after inpatient rehab

# Patient case

- Re-admitted 3 months later with toxic megacolon
- Taken to OR for colectomy

# Benefits of Enteral vs. Parenteral Nutrition

- For all patient populations, enteral nutrition generally considered preferred route due to decreased cost and infectious complications

- For AKI, 1 study demonstrated greater mortality, infection with PN
  - EN (n =45), mortality 42%, infection 64%
  - PN (n = 19), mortality 69%, infection 84%
    - (p = 0.05)

Nutrition 2004;20:843-848
JPEN 2009;33:277-316.
J Renal Nutr. 2008;18:288-293.

# Infection Risk of Parenteral Nutrition

- Incidence of TPN associated catheter-related bloodstream infections in critical care ranges from 1.5 – 21%

- A general hospitalized population found 1.4 – 2% per patient day rate of catheter-related sepsis

Clin Nutr. 2005 Apr;24(2):220-3.
J Microbiol Immunol Infect. 2006 Jun;39(3):231-6.
Clinical Infectious Diseases. 1998;27:500-3.

# Risk factors for invasive candidiasis

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## Host Factors

- Extremes of age
- Neutropenia
- **Renal failure**
- Higher APACHE II Score
- Trauma/burns
- Bowel perforation

## Medical intervention

- Chemotherapy
- **Dialysis**
- **Central venous catheters**
- Antibiotic use
- **Parenteral nutrition**
- **Abdominal surgery**
- Length of ICU stay > 7 days
- Nasogastric tubes
- Gastric acid suppression

Crit Care Med 2010 Vol 38, S380-387

# Factors independently associated with candidemia

| Prior surgery | RR 7.3 |
|---|---|
| Acute renal failure | RR 4.2 |
| Parenteral nutrition | RR 3.6 |
| Presence of TLC | RR 5.4 |

Clin Infect Dis 2001; 33:177-186.

# Conclusions

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- Enteral nutrition preferred over parenteral nutrition when possible
- Protein requirements are different for AKI vs CRF
- Protein requirements differ depending on dialysis modality
- Risks vs. benefits must be weighed in initiating parenteral nutrition

# Parenteral Nutrition in the Obese Patient

Erin Nystrom, Pharm.D., BCNSP
Clinical Pharmacist in Nutrition Support
Mayo Clinic
Rochester, Minnesota

# Conflicts of Interest

- No conflicts to disclose

# Learning Objectives

- Review the appropriate roles for both acute and chronic PN in obese patients
- Provide recommendations for dosing and monitoring of PN in patients with obesity
- Discuss potential complications of PN in patients with obesity

# Obesity

- Definitions
  - Excessive adipose tissue in relation to lean body mass
  - NIH/WHO classification
    - Obese: BMI ≥ 30 kg/$m^2$
      - Obese class I 30 – 34.9 kg/$m^2$
      - Obese class II 35 – 39.9 kg/$m^2$
      - Obese class III ≥ 40 kg/$m^2$
    - Overweight/Pre-obese: BMI 25 to 29.9 kg/$m^2$
- 33.8% of Americans are obese (CDC 2010)

## Trust for America's Health & Robert Wood Johnson Foundation:

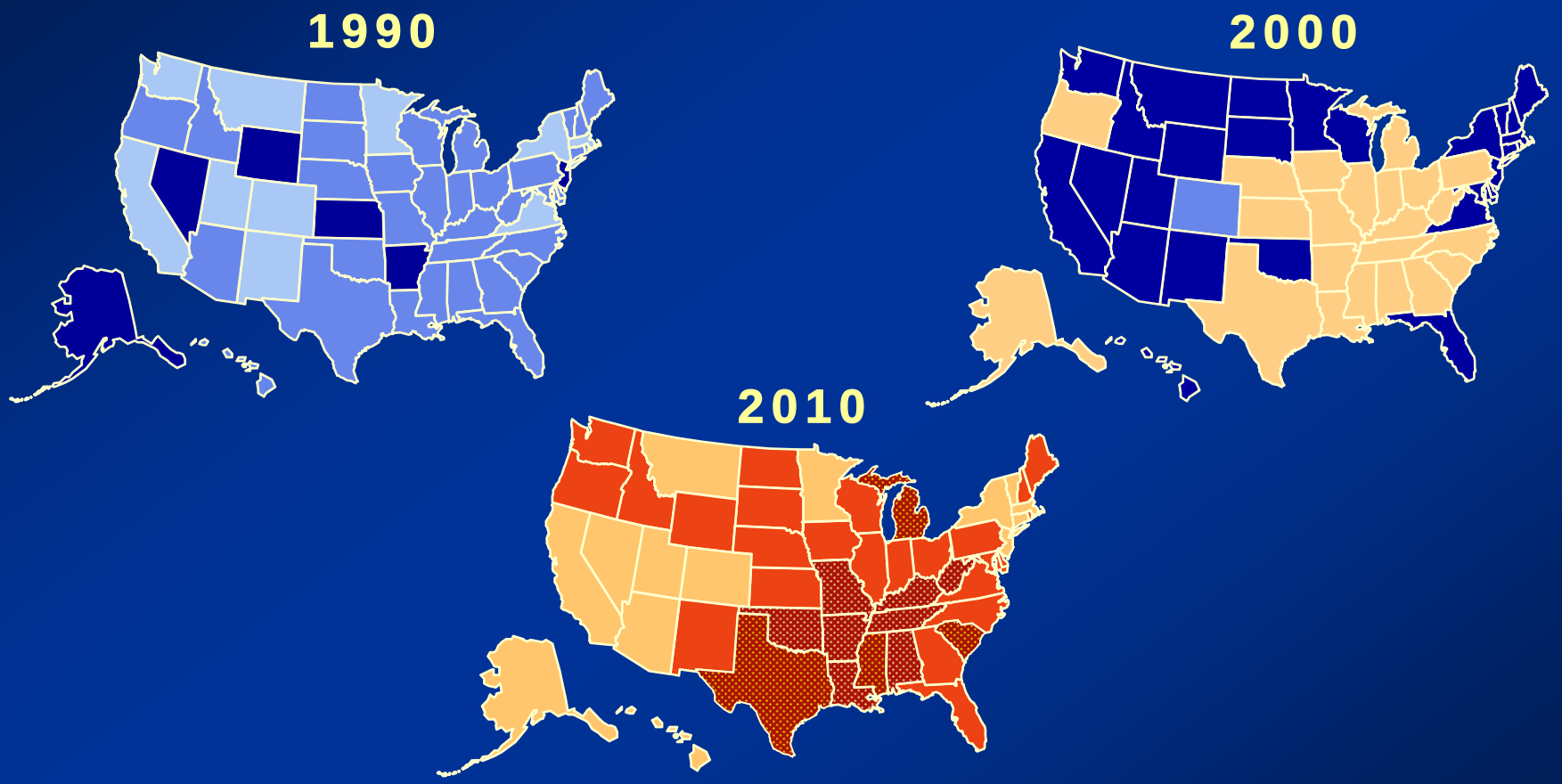
# F as in Fat 2011

- Two-thirds of adults and one-third of children are overweight or obese
- Since 2010, obesity rates increased in 16 states; 12 states over 30%
- In the last 15 years…
  - 7 states' obesity rates doubled
  - 10 states increased at least 90%
  - 22 states increased at least 80%

# Obesity Trends* Among U.S. Adults

## BRFSS, 1990, 2000, 2010

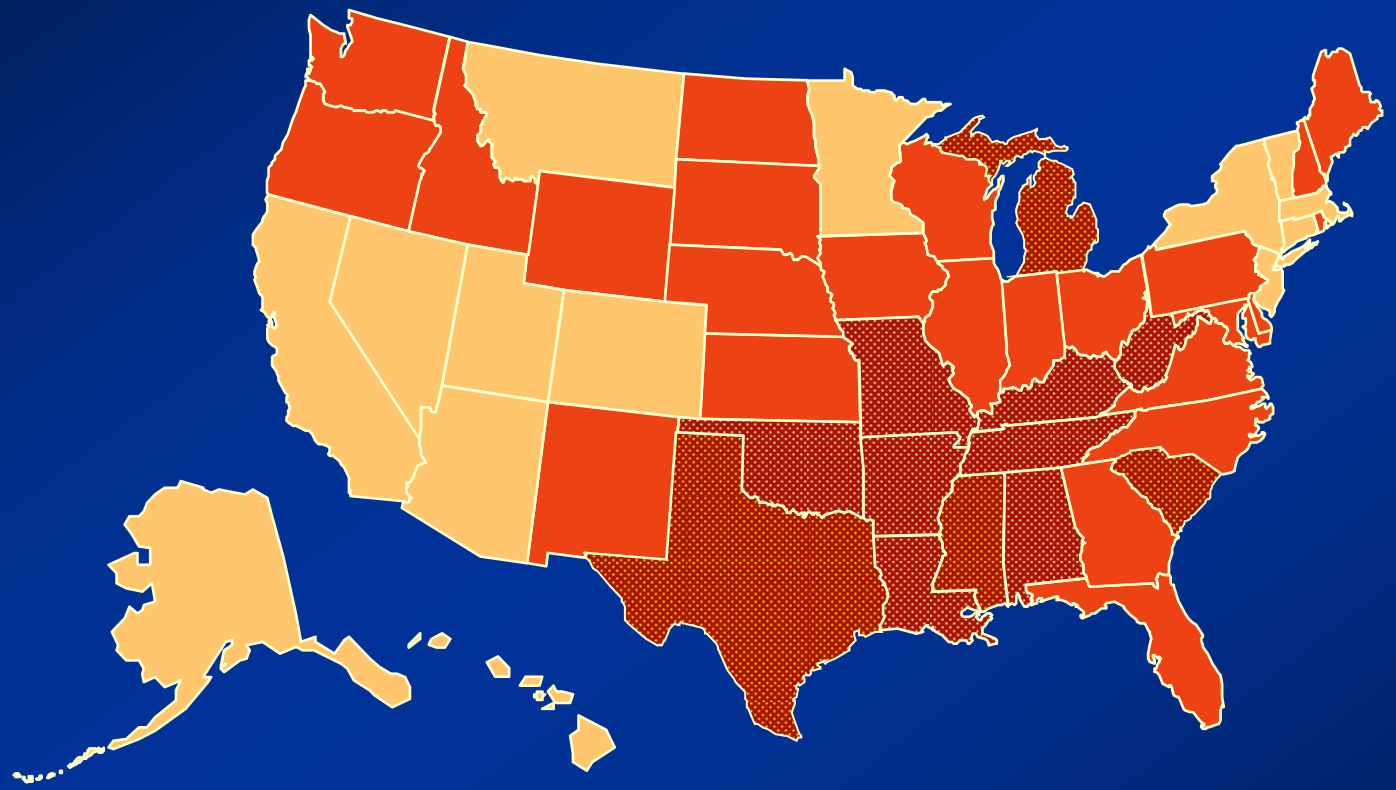
**(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)**




Source: Behavioral Risk Factor Surveillance System, Centers for Disease Control.

# Obesity Rates* Among U.S. Adults 2010

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



No Data | < 10% | 10%–14% | 15%–19% | 20%–24% | 25%–29% | ≥ 30%

Source: Behavioral Risk Factor Surveillance System, Centers for Disease Control.

# Obesity-Associated Morbidity

- TFAH/RWF 2011 Report
  - Type 2 Diabetes: Rates increased in 11 states in past year; 8 states with over 10% of adults
  - Hypertension: Every state over 20% of adults with hypertension; 9 states over 30%

# Obesity-Associated Morbidity

- Type 2 diabetes; insulin resistance
- Dyslipidemia
- Gastrointestinal
  - Nonalcoholic fatty liver disease: steatosis, nonalcoholic steatohepatitis
  - Gall stones, cholelithiasis
  - Pancreatitis
- Obstructive sleep apnea
- Osteoarthritis
- Cardiovascular
  - Hypertension
  - Coronary artery disease
  - Congestive heart failure
  - Stroke
  - Deep vein thrombosis, pulmonary embolism
- Cancer
  - Breast
  - Colon
  - Endometrium
  - Esophagus
  - Stomach

Rollinson, Shikora, Salzman et al. A.S.P.E.N. Nutrition Support Core Curriculum 2007.
AGA Medical Position Statement on Obesity. Gastroenterology 2002.

# PN in Obesity: Goals of Care

- Minimize risk of metabolic complications
  - Do No Harm
  - Metabolic Control
- Preserve lean body mass
- Promote gradual loss of fat tissue

- When, how much, what to monitor?

Dickerson et al. Am J Clin Nutr 1986.

# When to Initiate PN?

- Body weight is not a good indicator of underlying nutrition status
  - "Reserves" do not place a patient at lower nutritional risk
  - Acute illness vs. chronic starvation
- Risks of malnutrition: impaired wound healing, immune function, ventilator weaning and increased infection risk

# How Much to Feed?

- Body composition in obesity
  - Adipose tissue is metabolically inactive
  - Lean mass increases with weight gain; neither fat nor lean mass gain is linear with weight gain
  - Mobilization of fat stores in acute illness
  - Energy expenditure vs. requirement
- Feed to metabolic control

# Metabolic Complications: Risks of Overfeeding

- Hyperglycemia, glucose intolerance, hyperinsulinemia
- Volume overload
- Hypercarbia
- Hypertriglyceridemia
- Inflammation
- Impaired fat mobilization and oxidation
- Lipogenesis, hepatic steatosis
- Infection, immunosuppression

# Advantages of Hypocaloric, Protein-Sparing Feeding

- Reduced carbon dioxide production
- Reduced hyperglycemia, hyperinsulinemia
- Improved diuresis
- Enhanced wound healing and immune function

# How Much to Feed?

- Total energy expenditure
  - Resting/basal energy expenditure (REE/BEE) ~ 70%
  - Thermic effect of food ~ 10%
  - Physical activity ~ 20%
- REE greater in obesity
- Best way to estimate BEE?

# Predictive Equations
## (BEE, kcal/day)

- Harris Benedict
  - Females: 655 + 9.6(wt, kg) + 1.8(ht,cm) – 4.7(age, yr)
  - Males: 66.5 + 13.8(wt, kg) + 5(ht,cm) – 6.8(age, yr)
- Ireton-Jones
  - Ventilated: 1784 - 11(age, yr) + 5(wt, kg) + 244(S) + 239(T) + 804(B)
  - Spontaneous breathing: 629 – 11(A) + 25(W) – 609(O)

  S = sex (female = 0, male = 1), V = ventilator (absent = 0, present = 1);
  T = trauma (absent = 0, present = 1), B = burn (absent = 0, present = 1)
- Mifflin-St.Jeor
  - Females: 10(wt, kg) + 6.25(ht, cm) - 5(age, yr) - 161
  - Males: 10(wt, kg) + 6.25(ht, cm) – 5(age, yr) + 5
- 21 kcal/kg (Amato 1995)

# Which Weight to Use?

- Ideal weight (IBW), e.g., Hamwi
- Adjusted body weight
  - (Actual weight – IBW) x estimated LBM contribution + IBW
  - Lean body mass accrual is not linear with weight gain; lack of scientific data to support “adjustment” factor
- Weight measurement limitations in obesity

# Predicting Energy Expenditure

- Limitations of predicted energy expenditure trials
  - Indirect calorimetry
  - Healthy controls not included
  - Fed vs. fasting; degree of illness; other variables
  - Small numbers, heterogeneous
- Reported correlations between measured and predicted REE do not equal accuracy in the individual patient

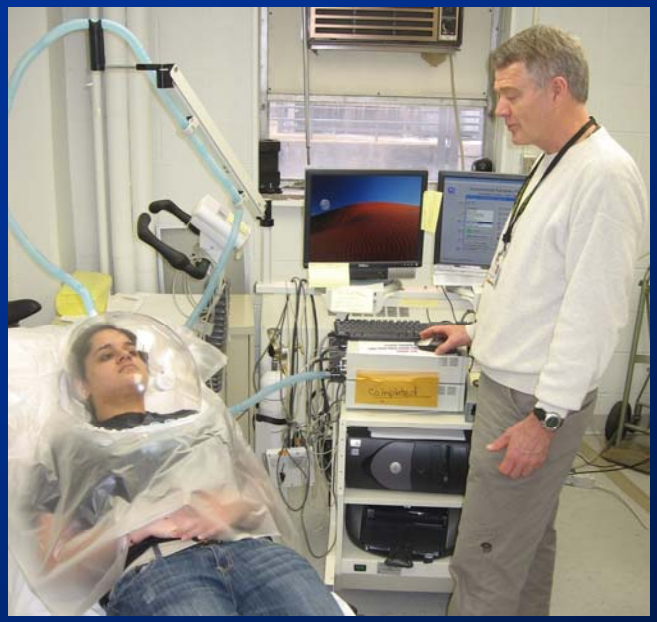
# Predicting Energy Expenditure

**ASPEN-SCCM, 2009**
**Nutrition in Critical Illness Guidelines:**

"Predictive equations should be used with caution, as they provide a less accurate measure of energy requirements than indirect calorimetry in the individual patient."

# Indirect Calorimetry: REE

- Measures O2 consumption and CO2 production
- Weir equation
  - REE (kcal/24h) = (3.9 $\dot{V}O_2$ + 1.1 $\dot{V}CO_2$) X 1.44
- Respiratory Quotient (RQ)
  - RQ = $\dot{V}CO_2$ / $\dot{V}O_2$
    - Validates IC if within physiologic range
    - CHO = 1
    - Pro = 0.8
    - Fat = 0.7
    - Lipogenesis = 1.1 – 1.2



http://www.icts.uiowa.edu/drupal/

# Indirect Calorimetry Limitations

- Point-in-time analysis
- Confounders
  - Activities/cares
  - Respiratory status
  - Acid/base disturbances
  - Air leaks
  - Fever, sepsis
- $FiO_2$ < 60%; no nasal cannula
- Operator experience
- RQ correlates with substrate use and under- or overfeeding, but low sensitivity, specificity
- Not widely available

# Parenteral Nutrition in Obesity: The Evidence

# Dickerson et al. 1986

- Thirteen obese surgical patients; Prospective, single-arm
- PN program: 50% REE as non-protein calories + protein of 2 g/kg (IBW)
  - Average: 881 npc/day + protein
  - PN duration:  48.2 +/- 31.4 (12 – 190) days
- Outcomes
  - RQ consistent with fat oxidation
  - Weight loss: 2.3 +/- 2.7 kg/wk
  - Nitrogen balance: all patients positive or even
  - All patients demonstrated complete tissue healing

# Burge et al. 1994

- Sixteen patients; Prospective, double-blind randomized trial
  - Hypocaloric group, n = 9: npc of 50% REE + protein 2 g/kg IBW
    - Avg 1285 kcal/day or 14 kcal/kg ABW
    - Avg 110 g protein
  - Control group, n = 7: npc of 100% REE + protein 2 g/kg IBW
    - Avg 2592 kcal/day or 25 kcal/kg ABW
    - Avg 130 g protein
  - PN duration: 9.6 +/- 3 (5 – 15) days
- Outcomes
  - RQ also consistent with oxidation of endogenous fat stores
  - N balance positive in both groups

# Choban et al. 1997

- Thirty patients; Randomized, double-blind study
  - Isonitrogenous formulas, 2 g/kg IBW
  - Hypocaloric, n = 16: kcal:N = 75:1 (33% kcal as protein)
    - 1292 +/- 298 kcal/d; 14 kcal +/- 3 kcal/kg ABW
  - Control, n = 14: kcal:N = 150:1 (17% kcal as protein)
    - 1934 +/- 198 kcal/d; 22 +/- 5 kcal/kg ABW
  - PN duration: 10.5 +/- 2.6 (6 – 15) days
- Results
  - No difference in N balance
  - Better glycemic control and lower insulin requirement in hypocaloric group

# State of the Data

- Total number of obese patients on PN studied = 89
  - Two RCTs (n = 46)
  - One retrospective study (n = 30)*
  - Two studies used indirect calorimetry to predict REE
- Non-protein calories vs. total calories

* Liu et al. Am Surgeon 2000.

# Macronutrient Balance

- Mixed fuel source is best
- Protein-sparing properties: dextrose, fat, and protein
  - Elwyn 1980: Brain requires about 125 g/day dextrose; else gluconeogenesis to meet obligatory glucose needs is achieved by muscle catabolism
  - Sparing lean mass can not occur independently of non-protein calorie provision
- Dextrose overfeeding in absence of fat promotes lipogenesis (Paluzzi, Meguid 1987)

# Unanswered Questions

- Clinical outcomes with hypocaloric, high protein regimens
- Specific patient populations
  - Kidney failure, renal replacement therapy
  - Liver disease; hepatic encephalopathy
  - Burns, trauma
  - Higher obesity classifications
  - Long-term PN
- Markers of adequacy of nutrition

# Surrogate Markers vs. Clinical Outcomes

- Koretz RL, Proc Nutr Soc 2005.
- Reviewed 99 RCTs of nutrition support vs. no nutrition support and clinical outcome vs. surrogate marker association
- Surrogate
  - Albumin
  - Transferrin
  - Prealbumin
  - Nitrogen balance
- Clinical
  - Mortality
  - Infections
  - Total complications
  - Hospital length of stay

| | Concord-ance (%) | Partial Discordance (%) | | Complete Discordance (%) | |
|---|---|---|---|---|---|
| | | Nutrition better | Clinical better | Nutrition better | Clinical better |
| **Albumin** | | | | | |
| Mortality | 29 | 18 | 20 | 25 | 9 |
| Infections | 38 | 16 | 8 | 32 | 5 |
| **Prealbumin** | | | | | |
| Mortality | 33 | 39 | 6 | 22 | 0 |
| Infections | 38 | 6 | 0 | 56 | 0 |
| **N Balance** | | | | | |
| Mortality | 36 | 42 | 0 | 22 | 0 |
| Infections | 43 | 17 | 0 | 40 | 0 |

# Minnesota Starvation Experiment

- Conducted by University of Minnesota from Nov.1944 to Dec. 1945
- 32 male participants; 3 phases, including 24-week 'semi-starvation' phase

| | Baseline* | 6 mos* |
|---|---|---|
| Weight | 69.4 ± 5.9 | 52.6 ± 4.0 |
| BMI | 21.7 ± 1.7 | 16.4 ± 0.9 |
| Albumin | 4.3 ± 0.5 | 3.9 ± 0.5 |

* Mean ± standard deviation.

Keys et al. The Biology of Human Starvation 1950.

# Visceral Proteins

| | Albumin | Prealbumin (Transthyretin) |
|---|---|---|
| Half-life | 20 days | 2-3 days |
| Normal | 3.5-5 g/dL | 10-15 mg/dL |
| Factors that **Increase** Levels | Dehydration<br>Exogenous albumin | Corticosteroids<br>Renal failure<br>Dehydration |
| Factors that **Decrease** Levels | **Stress/Acute Phase Response**<br>Volume overload<br>Liver disease | **Stress/Acute Phase Response**<br>Dialysis<br>Liver disease |

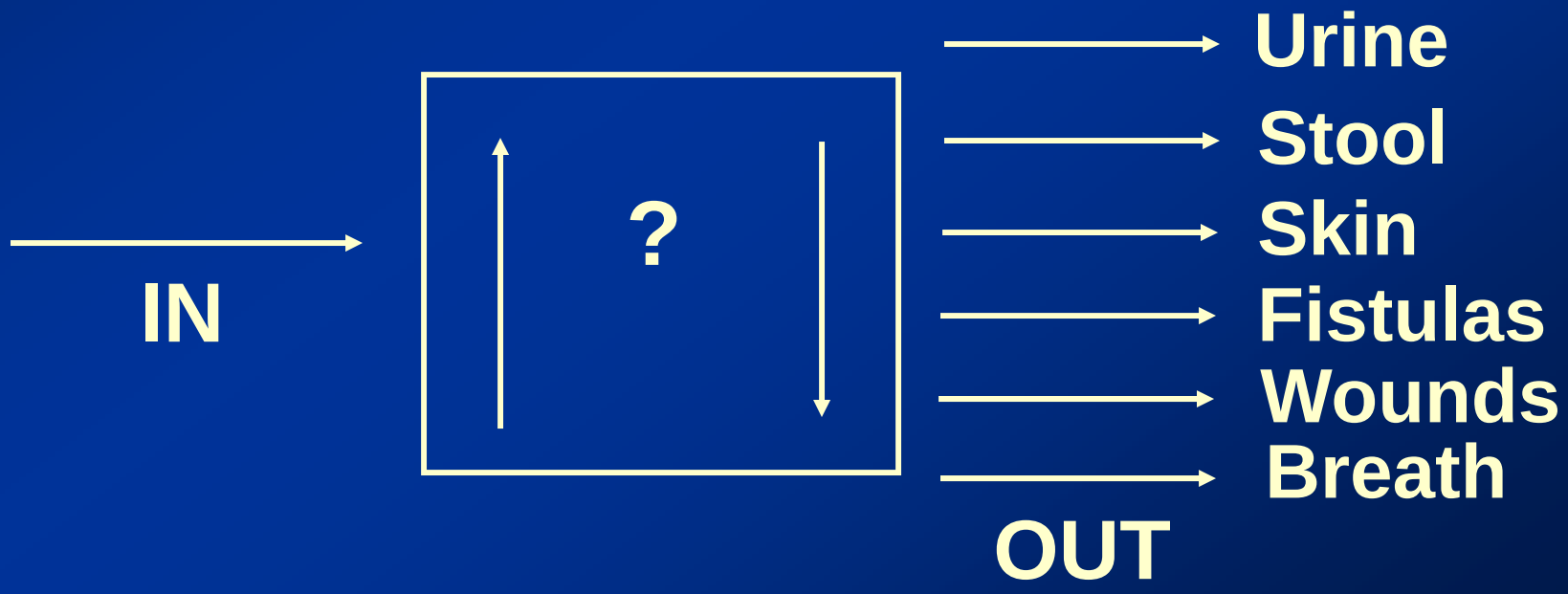
**Hepatic proteins are better indicators of inflammation and severity of illness**

# Nitrogen Balance

N balance = $N_{in}$ minus $N_{out}$

= (g pro/6.25) - (UUN + 4)

**N balance is not N utilization**




Slide: Adapted from M. Kochevar.

# N Balance Limitations

- 24-hour urine collection; requires steady state
- Unaccounted nitrogen losses
- Factors that alter urine urea nitrogen (UUN) content
  - Renal disease
  - Liver disease, hyperammonemia
  - Stress, protein catabolism
  - Preexisting state of nutrition
  - Acidosis
  - Hematuria, bacteruria

# PN in Obesity

- Data support
  - Fat stores are mobilized in acute illness
  - Underfeeding is effective
    - Preservation of lean body mass (N balance)
    - Successful wound healing
  - Underfeeding reduces metabolic complications
- More research needed

# Best Practice

- Matching energy expenditure risks overfeeding
- Hypocaloric, high-protein regimen
  - Protein 1.5 - 2 g/kg ideal weight
  - 60 – 75% of BEE/REE; daily calorie deficit
- Indirect calorimetry?
- ASPEN/SCCM Guidelines in ICU
  - Protein of 2 – 2.5 g/kg ideal weight
  - Avoid exceeding 60 – 70% energy requirements or 11 – 14 kcal/kg actual weight

SCCM-A.S.P.E.N., JPEN 2009.
Miles JM. Mayo Clin Proc 2006.

# Case

GL, 52 y/o male admitted with 1-week history of N/V/abdominal pain, found to have SBO. PMH: Crohn's disease, hyperlipidemia, hypertension, osteoarthritis.

Wt: 92 kg Ht: 179 cm

BMI: 29.6

IBW: 76.7 kg

Harris Benedict BEE: 1917 kcal/day

PN Program?

Monitoring parameters?

# Case: PN Program

- Energy/Protein: 75% HB = 1400 - 1450 kcal/day; includes protein of 1.5 – 2 g/kg IBW or 115 – 150 g/day
- PN Program: 120 g protein, 150 g dextrose, 40 g fat
- Monitor: Glucose, triglycerides
- Day 3 PN: TG = 390… Next step?
- What if hyperglycemia?

# Summary

- Nutrition prescription in the obese patient warrants an individualized approach
- Predictive equations lack validation in obesity, but are a starting point for estimating energy expenditure
- Hypocaloric, high-protein approach is recommended to minimize overfeeding risks
- Close monitoring is essential to optimize metabolic control
- More research is needed to define optimal energy prescription and markers of adequacy of nutrition support

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# Micronutrient Supplementation and Long Term Adverse Effects of TPN Therapy

**Leslie A. Hamilton, Pharm.D., BCPS**

**10/18/2011**

# Conflicts of Interest

American College of Clinical Pharmacy

- No conflicts of interest to report.

# Objectives

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- Review the role and appropriateness of micronutrient supplementation in patients receiving TPN therapy.
- Provide recommendations for dosing and monitoring of micronutrient supplementation in acute and chronic TPN therapy.
- Discuss strategies for prevention and management of long term adverse effects of TPN therapy.

# Trace Elements

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- Given daily as a mixture of four to five trace elements
- Trace elements can also be given individually for supplementation
- Direct antioxidant activity and cofactors for antioxidant enzymes

# Requirements

| Trace Element | Preterm Neonates (<3 kg) (mcg/kg/d) | Term Neonates (3 – 10 kg) (mcg/kg/d) | Children (10 – 40 kg) (mcg/kg/d) | Adolescents Standard Daily Intake (>40 kg) | Adult Standard Daily Intake |
|---|---|---|---|---|---|
| Zinc | 400 | 50 – 250 | 50 – 125 | 2.5 – 5 mg | 2.5 – 5 mg |
| Copper | 20 | 20 | 5 – 20 | 0.2 – 0.5 mg | 0.3 – 0.5 mg |
| Manganese | 1 | 1 | 1 | 40 – 100 mcg | 60 – 100 mcg |

# Requirements

American College of Clinical Pharmacy

| Trace Element | Preterm Neonates (<3 kg) (mcg/kg/d) | Term Neonates (3 – 10 kg) (mcg/kg/d) | Children (10 – 40 kg) (mcg/kg/d) | Adolescents Standard Daily Intake (>40 kg) | Adult Standard Daily Intake |
|---|---|---|---|---|---|
| Chromium | 0.05 – 0.2 | 0.2 | 0.14 – 0.2 | 5 – 15 mcg | 10 – 15 mcg |
| Selenium | 1.2 – 2 | 2 | 1 – 2 | 40 – 60 mcg | 20 – 60 mcg |

# Adult Products

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| Trace Element | Amount per unit dose | | | | |
|---|---|---|---|---|---|
| Manufacturer | American Regent | | | | Hospira |
| | Multitrace-5 Concentrate | Multitrace-5 | Multitrace-4 Concentrate | Multitrace-4 | 4-Trace Elements |
| Zinc | 5 mg | 1 mg | 5 mg | 1 mg | 4 mg |
| Copper | 1 mg | 0.4 mg | 1 mg | 0.4 mg | 1 mg |
| Manganese | 0.5 mg | 0.1 mg | 0.5 mg | 0.1 mg | 0.8 mg |
| Chromium | 10 mcg | 4 mcg | 10 mcg | 4 mcg | 10 mcg |
| Selenium | 60 mcg | 20 mcg | None | None | None |

# Pediatric Products

American College of Clinical Pharmacy

| Trace Element | Amount per unit dose | | |
|---|---|---|---|
| Manufacturer | American Regent | | |
| | Multitrace-4 Neonatal | Trace Elements Injection 4 Pediatric | Multitrace-4 Pediatric |
| Zinc | 1.5 mg | 0.5 mg | 1 mg |
| Copper | 0.1 mg | 0.1 mg | 0.1 mg |
| Manganese | 25 mcg | 30 mcg | 25 mcg |
| Chromium | 0.85 mcg | 1 mcg | 1 mcg |
| Selenium | None | None | None |

# Zinc

- Reduced gastric acidity decreases zinc availability for absorption
- Most zinc is intracellular
- Mostly absorbed in duodenum and jejunum
- Transported by albumin to the liver
- Hypoalbuminemia can impair hepatic release of zinc

# Zinc

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Zinc homeostasis affected by:

- Dietary zinc intake
- Fasting
- Acute infection
- Minerals and vitamins
- Alcohol
- Calcium and milk proteins
- Copper and iron competition

# Zinc

- Catalyst for more than 200 enzymes
- Involved in apoptosis, cellular proliferation and differentiation, and immune function

# Zinc Deficiency

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- Difficult to diagnosis
  - Redistributed during acute phase response
- Skin lesions
- Impaired night vision
- Anorexia
- Diarrhea
- Impaired immune function
- Impaired wound healing

# Zinc Deficiency

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- Decreases retinol mobilization from the liver
- Decreased in elderly, alcoholics, post-operative and burn patients, patients with malabsorption, and renal disease
- Can worsen respiratory muscle function, hepatic dysfunction, and glucose intolerance

# Zinc Toxicity

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- Gastric distress
- Nausea
- Dizziness
- Decreased immune function
- Decreased HDL
- High doses can induce copper deficiency

# Zinc

- In SIRS, also draw a CRP level
  - Will help determine if acute phase reaction or increased zinc requirements
- Serum zinc levels < 70 mcg/dL:  low
- Serum zinc levels 70 – 85 mcg/dL:  marginal zinc status

# Zinc

- Extra zinc should be given to patients with high-output ostomies, chronic diarrhea, and thermally burned patients receiving PN
  - Zinc 12 mg can be added per liter of gastrointestinal loss
  - Up to 36 mg per day of zinc has been given to benefit patients with severe burns without toxicity

# Copper

- Digestion releases copper to free it for absorption
- Gastric secretions, HCl, and pepsin assist in release of bound copper in the stomach
- Most absorption occurs in the small intestine, mostly in the duodenum

# Copper

- Absorption negatively affected by:
  - Dietary fiber
  - Zinc
  - Iron
  - Large doses of calcium gluconate
  - Large doses of vitamin C
  - $H_2$ antagonists and PPI's
- Transported by albumin
- Involved in iron transfer

# Copper

- Responsible for:
  - Manganese oxidation
  - Ferrous and ferric iron oxidation
  - Conversion of dopamine to norepinephrine
  - Cholesterol and glucose metabolism

# Copper Deficiency

- Microcytic anemia
- Leukopenia
- Neutropenia
- Hypercholesterolemia
- Abnormal ECG
- Menkes disease
- Occurs in patients with chronic diarrhea, post-intestinal surgery, and in chronic HD

# Copper Toxicity

- Uncommon, except in impaired biliary excretion or cholestasis
- Wilson's disease (cirrhosis)

# Manganese

- Competes with iron for binding sites
- Enters liver via portal circulation
- Almost 100% is excreted via bile into feces
- Part of metalloenzymes
  - Arginase (urea formation)
  - Pyruvate carboxylase (carbohydrate synthesis)
  - Mn superoxide dismutase (antioxidant)

# Manganese Deficiency

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- Rare
- Reproductive difficulties
- Abnormal bone and cartilage formation
- Defects in lipid and carbohydrate metabolism

# Manganese Toxicity

- CNS abnormalities
  - Hallucinations
  - Ataxia
  - Hyperirritability
  - Parkinson-like
- Reproductive dysfunction
- Nephritis
- Hepatic Damage

# Manganese Toxicity

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- Risk
  - Long-term PN ( > 30 days)
  - Biliary tract obstruction
- Difficult to determine manganese status
  - Whole blood manganese levels
  - MRI
- Contamination product from calcium gluconate, magnesium sulfate, and potassium chloride

# Manganese and Cholestasis

- IV Manganese delivery bypasses normal regulatory mechanism
- Predisposes long-term PN patients to tissue and/or brain accumulation of Manganese

# Chromium

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- Required for glucose and lipid metabolism
- Poor absorption
  - 0.4 – 3%
- Transported with iron
- Competes for binding sites with transferrin

# Chromium Deficiency

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- Impaired glucose and amino acid utilization
- Increased plasma LDL
- Peripheral neuropathy
- Only seen in PN patients without adequate chromium replacement
- Weight loss
- Hyperglycemia refractory to insulin

# Chromium Toxicity

- Rhabdomyolysis (1200 mcg/day)
- Liver dysfunction
- Renal failure (600 mcg – 2400 mcg/day)
- Compromised iron status
  - Ferritin decreases with chromium intake of 200 mcg/day

# Chromium Levels

- Serum:  0.05 – 0.5 mcg/L
- Erythrocyte:  20 – 36 mcg/L
- Urine:  0.1 – 2 mcg/L

# Chromium

- Levels are decreased in critically ill patients and during acute infection
- Some literature of using chromium infusions in critically ill patients with extreme insulin resistance
  - One case report of 3 mcg/hour (100 mcg of elemental chromium) in a patient requiring > 2000 units of insulin
  - Insulin requirements dropped dramatically and insulin infusion was discontinued within 12 hours

# Selenium

- Excreted renally and through fecal excretion
- Cofactor in glutathione, iodine, and thyroid metabolism
  - Eliminate hydrogen peroxide
  - Catalyze deiodination of iodine
  - Oxidative defense

# Selenium Deficiency

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- Oxidative injury
- Increased susceptibility to mercury injury
- Altered thyroid hormone metabolism
- Increased glutathione levels
- Keshan disease (cardiomyopathy)

# Selenium Toxicity

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- Nausea/vomiting
- Fatigue
- Tooth decay
- Hair and nail loss
- Peripheral neuropathy

# Selenium

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- Additional selenium (60 – 100 mcg/day) should be given to home PN patients
- Erythrocyte levels < 10.5 U/mL suggests deficiency
- Serum levels > 100 mcg/L suggest adequate selenium status

# Selenium

- Often depleted in trauma and SIRS patients
  - Additional supplementation has been studied at doses from 155 – 400 mcg/day
- Trend toward reducing mortality in sepsis and septic shock

# Contamination

- Many PN components are contaminated with trace elements:
  - Aluminum
  - Chromium
  - Copper
  - Manganese
- Patients on long-term PN are at higher risk of toxicities and should have serum monitoring

# Iron

- Iron is not routinely added to PN formulations
  - Cannot be added to PN with IVFE as it causes destabilization of IVFE
  - Can be added to Two-in-One formulations

# Liver Disease and Trace Elements

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- Remove copper and manganese from PN for patients with hepatobiliary disease
  - Elevated direct and total bilirubin levels
- Advanced liver disease is often accompanied by zinc deficiency
  - Replacement may improve amino acid metabolism and grade of encephalopathy

# Renal Disease and Trace Elements

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- Chronic HD can deplete copper stores
- Zinc is often depleted in renal disease
- Selenium is often depleted in CKD patients
- Selenium, chromium, copper, and zinc are removed by CRRT

# Burn Injury

- May benefit from additional selenium
  - Reports of 210 mcg/day to maintain balance
  - Up to 380 mcg/day to help prevent nosocomial pneumonia
- Additional zinc is beneficial
- Improves wound healing, reduces infections

# Fistulas

- Additional zinc supplementation is needed, especially for high-output fistulas
  - 12mg of zinc/liter lost

# Bariatric Surgery

- Biliopancreatic diversion or duodenal switch
  - Additional zinc supplementation is needed

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